THE SURGICAL CLINICS OF NORTH AMERICA

FEBRUARY 1979

ENDOCRINE SURGERY

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SYMPOSIUM ON
ENDOCRINE SURGERY

Steven G. Economou, M.D., *Guest Editor*

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ERRATUM

An error was made in Table 1 on page 1293 of Dr. Basil A. Pruitt's article on "Fluid and Electrolyte Replacement in the Burned Patient" which appeared in the December 1978 issue. In the last column in Table 1 (glucose in water during the second 24 hours), 2000 ml of glucose in water belongs under the Brooke formula, *not* the Parkland formula.

RECENT SYMPOSIA

April 1978
ORGAN TRANSPLANTATION

June 1978
COLON AND ANORECTAL SURGERY

August 1978
BREAST CANCER

October 1978
PERSONAL PERSPECTIVES IN SURGERY

December 1978
BURNS

FORTHCOMING SYMPOSIA

April 1979
SURGICAL ASPECTS OF IMMUNOLOGY
RICHARD L. SIMMONS, M.D., *Guest Editor*

June 1979
ADVANCES IN HOSPITAL CARE
CHARLES M. ABERNATHY, M.D., *Guest Editor*

August 1979
PERIPHERAL VASCULAR SURGERY
JOHN A. MANNICK, M.D., *Guest Editor*

Contents

Foreword 1

Steven G. Economou

Aspiration Biopsy Cytology (ABC) in Tumors of the Thyroid Gland Suspected to Be Malignant 3

Torsten Löwhagen, Per-Ola Granberg, Göran Lundell, Pekka Skinnari, Rolf Sundblad, and Jan-Silvester Willems

Fine needle aspiration biopsy cytology (ABC) of the thyroid using smears of the aspirated material has been employed with great accuracy in Sweden since the 1950's to distinguish between benign and malignant lesions. The authors explain the technique, which avoids unnecessary diagnostic operations, is quick and inexpensive, and does not give false positive results.

The Ultrasound of Thyroid Masses 19

Irving B. Rosen, Paul G. Walfish, and Murray Miskin

Ultrasonography provides an accurate, noninvasive method of differentiating between cystic, solid, and mixed lesions. Using the described technique, patients with cystic lesions can be conservatively managed, and response to treatment can be measured by serial examinations.

Reemergence of Thyroidectomy as Treatment of Graves' Disease 35

Peter Klementschitsch, Kuo-liang Shen, and Edwin L. Kaplan

Because anti-thyroid drugs are effective in achieving remission from Graves' disease in only one-third of

patients, and because radioactive iodine therapy carries a long-term carcinogenic risk, subtotal thyroidectomy is reemerging as the treatment of choice. The authors describe the operation and review the indications and risks.

The Approach to the Irradiated Thyroid 45

Thomas R. Witt, Ronald L. Meng, Steven G. Economou, and Harry W. Southwick

Nodular thyroid disease and cancer are frequently associated with a history of prior irradiation. Mass screening and patient recall programs have identified those at risk. Treatment involves careful evaluation followed by total or near-total thyroidectomy for patients with cancer.

Radiation Exposure and the Simultaneous Occurrence of Primary Hyperparathyroidism and Thyroid Nodules 65

Ronald H. Nishiyama, Diane Farhi, and Norman W. Thompson

Exposure to radiation has been implicated in the unexpectedly high occurrence of primary hyperparathyroidism and simultaneous nonmedullary thyroid carcinomas. The authors review the evidence and suggest ways of evaluating patients for both conditions, including obtaining a careful history of radiation exposure, and periodic reevaluation of those exposed.

Parathyroid Surgery 77

Caldwell B. Esselstyn, Jr.

The controversy over how much parathyroid tissue to remove has been resolved by a consensus to individualize treatment according to the extent of disease. Autotransplantation of parathyroid tissue now reduces hypocalcemia following operation.

Prevention and Management of Complications Associated with Thyroid and Parathyroid Surgery 83

Anthony J. Edis

Complications following thyroid and parathyroid operations include paralysis of the vocal cords, scarring, postoperative hypocalcemia, and persistent hyperparathyroidism. This article reviews the major complications and suggests ways to minimize or prevent them.

The APUD Cell System and Its Neoplasms 93

Victor E. Gould, Vincent Memoli, Gregorio Chejfec, and Jan V. Johannessen

The idea that some endocrine cells populating the gastrointestinal tract and some viscera embryologically derived from it may be related to neural tissues has stimulated much needed research in endocrine pathology. The authors suggest the explanation of some puzzling phenomena such as production of "ectopic" hormones by some neoplasms in light of the APUD system theory, and propose directions for future clinical observation and research.

Multiple Endocrine Neoplasia Type IIB 109

Jeffrey A. Norton, Lynn C. Froome, Ruth E. Farrell, and Samuel A. Wells, Jr.

The combined clinical anomalies and common neuroectodermal origin of this most aggressive form of medullary thyroid carcinoma have been recognized only recently. A description of the syndrome and five case reports sum up the most recent conclusions.

Recent Advances in the Diagnosis and Treatment of Insulinomas 119

Edwin L. Kaplan and Chen-Hsen Lee

The ability to measure plasma insulin concentration by radioimmunoassay has greatly aided in the diagnosis of insulin-secreting tumors of the pancreas, but differentiation of these from other hypoglycemic states may still be difficult. The authors review the state of the art of diagnosis, localization, and treatment of insulinomas.

Pancreatic Islet Cell Tumors: Insulinoma, Gastrinoma, and Glucagonoma 131

George A. Higgins

The author describes the three major clinical syndromes associated with islet cell tumor and suggests surgical and nonsurgical techniques for the treatment of each condition. The article includes a review of recent developments in diagnostic testing.

Uncommon Tumors of the APUD System 143

Philip A. Visser and Stanley R. Friesen

In the last 10 years our understanding of hormone hypersecretions has been increased by the description

of secreting cells in the brain and in the gut by their common cytochemical characteristics of *A*mine *P*recursor *U*ptake and *D*ecarboxylation, thus suggesting their common origin in neuroectoderm. This article reviews diarrheogenic syndromes, somatostatinomas, paragangliomas, and other anomalies of the APUD system.

Cushing's Disease: The Role of Adrenalectomy and Autotransplantation 159

Richard A. Prinz, Marion H. Brooks, Ann M. Lawrence, and Edward Paloyan

Although the authors reaffirm the place of bilateral adrenalectomy as the cornerstone of treatment for Cushing's disease, they deplore the permanent adrenal insufficiency it engenders. In this article they describe the new technique of autotransplant of adrenal cortical tissue, which they have used successfully to alleviate adrenal insufficiency.

Transplantation of the Parathyroid Glands: Current Status 167

Samuel A. Wells, Jr., Arthur J. Ross, III, Janet K. Dale, and Roberta S. Gray

An experimental technique for transplantation of the parathyroid has been developed recently to counter renal osteodystrophy, primary parathyroid hyperplasia, and other unique problems of parathyroid hyperfunction. Operative procedure, postoperative management, assessment of graft function, and cryopreservation of parathyroid tissue are among the topics covered.

Index 179

Foreword

The field of surgery has steadily evolved to a point where the surgeon is no longer a mere technician or one whose excellence is measured solely by his virtuosity with the scalpel. This is especially true of the surgeon who treats patients with disorders of the endocrine organs. Knowing why, when, and on what to operate requires an ever broader understanding of the constellation of endocrine system abnormalities. Couple with this the considerable operative skills necessary for the successful conclusion of a series of logical clinical steps and it is not surprising that endocrine surgery is so fulfilling.

An important part of the currently intense interest in endocrine surgery is the swift evolution of unifying concepts of endocrine diseases, some hitherto unknown, yet most quite familiar but whose interrelationships were not properly appreciated. It is for this reason that a significant portion of this issue is devoted to the APUD system. An equally gratifying advancement has been the refinement of diagnostic and operative techniques so that a successful outcome is expected rather than just hoped for.

It was with specific intent and considerable pleasure that I invited a number of nonsurgeons to participate in this issue of the *Surgical Clinics*. This gesture was meant to underscore the need for multiple disciplines to focus on these singular yet multifaceted problems. The thoughts of these eminent authorities mesh naturally throughout this issue.

The one who synthesizes this knowledge and brings it to fruition enjoys the ultimate thrill. I am particularly pleased, therefore, and our readers are indeed fortunate, to have in this volume the contributions of internationally renowned surgeons of broad experience and high technical skill.

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Guest Editor

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Aspiration Biopsy Cytology (ABC) in Nodules of the Thyroid Gland Suspected to be Malignant

Torsten Löwhagen, M.D., Per-Ola Granberg, M.D.,†*
Göran Lundell, M.D.,‡ Pekka Skinnari, M.D.,§
*Rolf Sundblad, M.D.,¶ and Jan-Silvester Willems, M.D.***

Thyroid nodules often present diagnostic difficulties. The risk of carcinoma of the thyroid gland is higher if the nodule is solitary. Scintigraphy of the thyroid gland can be helpful, as a malignant tumor is rare in a hot nodule but is often found in a cold nodule.

The frequency of carcinoma in a cold solitary nodule has been reported to be around 20 per cent.[12, 14] The figure is somewhat higher in men than in women. Newer techniques with ultrasonic scanning, angiography, thermography, selenomethionine scanning, and so on have all failed to distinguish with certainty between benign and malignant lesions.

Needle biopsy with both large bore and fine needle aspiration has also been used. There have been and still are many objections against these diagnostic techniques. In three modern monographs on the thyroid,[2, 7, 9] the needle biopsy technique is not considered to be a substitute for open biopsy and it is suggested that needle biopsy should play no part in the investigation of a thyroid nodule. Fine needle aspiration biopsy is even considered to be abandoned.[7]

Fine needle aspiration biopsy cytology (ABC) of the thyroid has been used in Sweden since the beginning of the 1950s.[4, 15] More than 1500 ABC's are done on patients with thyroid problems each year at our hospital, and some 18,000 aspiration biopsies of the thyroid have been carried out during the last 20 years at the Karolinska Hospital. In spite of many publications of its accuracy,[1, 4, 8, 11, 15, 19] physicians outside Scandinavia have seemed reluctant to adopt ABC as a technique for the assessment of thyroid nodules.

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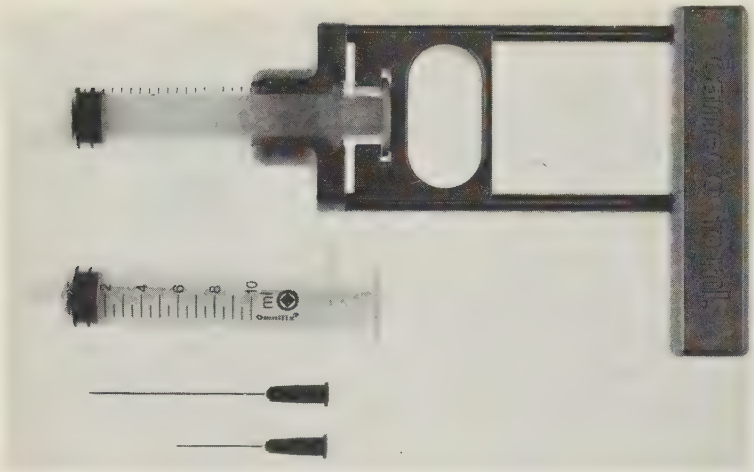

Figure 1. ABC instrumentarium.

This paper presents the technique we use in ABC and our interpretation of reading the slides, points out the differences between fine needle aspiration biopsy versus big needle biopsy with Vim-Silverman or Tru-Cut needles, and defines the accuracy of the ABC method in 412 patients with thyroid nodules suspected to be malignant.

ABC TECHNIQUE

The puncture of thyroid nodules is best performed with the patient in supine position with the neck moderately extended. No anesthesia is required, not even in children. The instrument required for aspiration biopsy is a fine needle adapted to a disposable syringe in a holder. This unit requires only one hand, so the free hand may steady and fix the nodule (Fig. 1). Disposable fine needles (22-gauge, 0.6 mm) are recommended.

SAMPLE TECHNIQUE. Figure 2 describes the technique of aspiration biopsy. The needle is introduced into the lesion with the handle in the resting state (Fig. 2*A*). The plunger is retracted to create a vacuum in the syringe (Fig. 2*B*). The needle is moved back and forth in different directions under constant suction in order to detach the tissue fragments (Fig. 2*C*). The plunger is released to eliminate the vacuum in order to reach a pressure equilibrium in the system (Fig. 2*D*). *Only then* is the needle withdrawn from the lesion, thereby avoiding aspiration of material into the syringe (Fig. 2*E*).

EXPELLING BIOPSY MATERIAL. Figure 3 describes the technique for expelling the biopsy material onto the microscopic slide. The needle containing the sample is detached from the syringe (Fig. 3*A*). The plunger is withdrawn to allow air into the syringe (Fig. 3*B*). The needle is reattached to the syringe (Fig. 3*C*). The needle content is blown out on a microscopic slide by pushing down the plunger, as the needle top touches the glass (Fig. 3*D*).

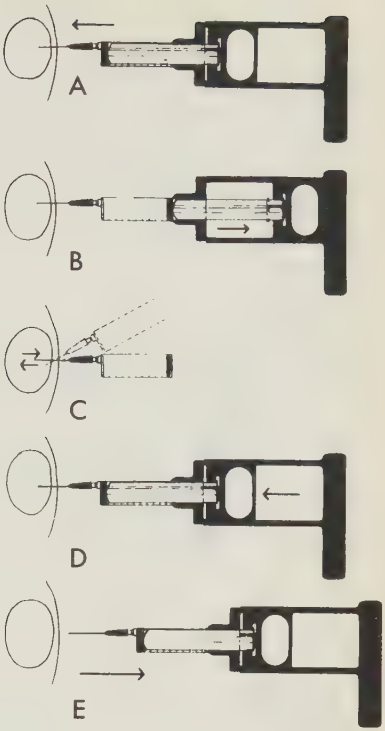

Figure 2. ABC sampling technique.

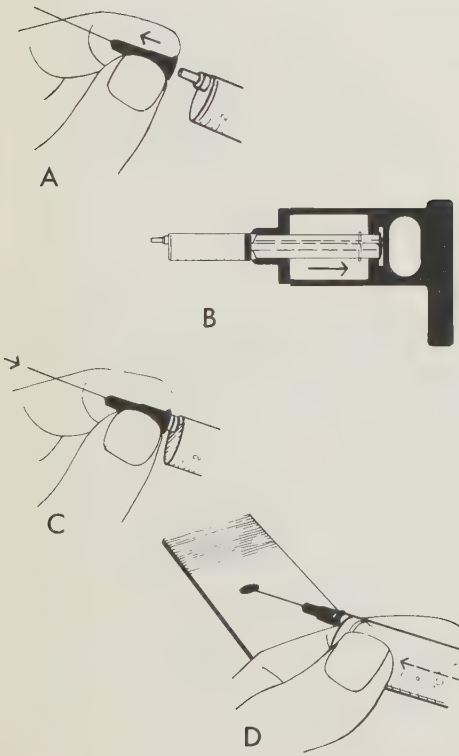

Figure 3. Transfer of aspirated cells to the glass slide.

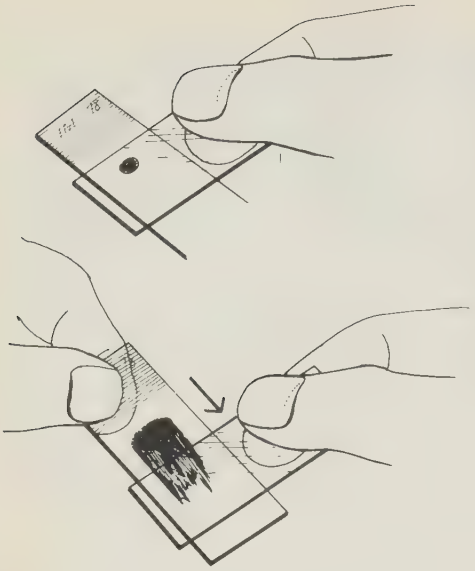

Figure 4. Smear preparation.

MAKING AND STAINING SMEARS. If the specimen is a semisolid droplet, it is gently squeezed with another slide followed by exerting slightly increasing pressure as described in Figure 4. If cystic degeneration within the nodule occurs, as much of the fluid as possible should be aspirated and investigated with the smear technique directly or after centrifugation and/or filtration.

The smear is air dried and stained according to the method of May-Grünwald-Giemsa, i.e., stains used for air-dried blood and bone marrow smears.

ABC VERSUS OTHER TECHNIQUES OF NEEDLE BIOPSY

ABC is often confused with needle biopsy using Vim-Silverman or Tru-Cut needles. It is, however, essential to separate the methods as they are based on different principles. With Vim-Silverman or Tru-Cut needles (Figs. 5 and 6), a piece of the tissue is cut out from the parenchyma for *histologic* examination. In ABC a *smear* is made of the aspirate for cytologic examinations.

While needle tract implantation has been reported rarely in patients with advanced or inoperable malignant tumors when the large bore needle technique was employed,[3, 11, 16] we have not seen it with the fine needle aspiration biopsy technique. Experimental studies by Engzell and coworkers showed that needling of lymph nodes with metastatic cancer did not increase the release of cancer cells into efferent lymphatics in animal models.[5]

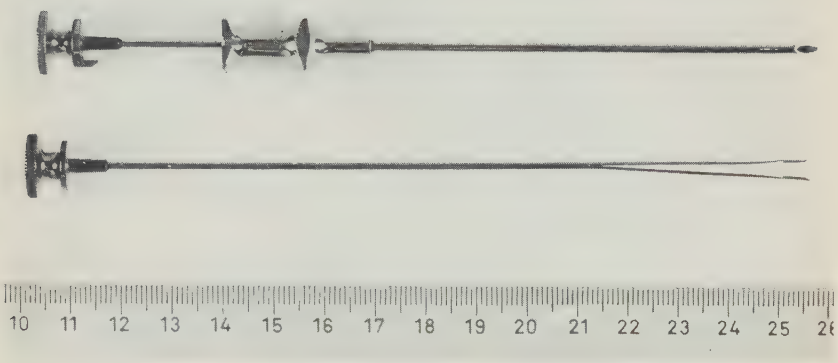

Figure 5. Vim-Silverman needle (cm per mm scale).

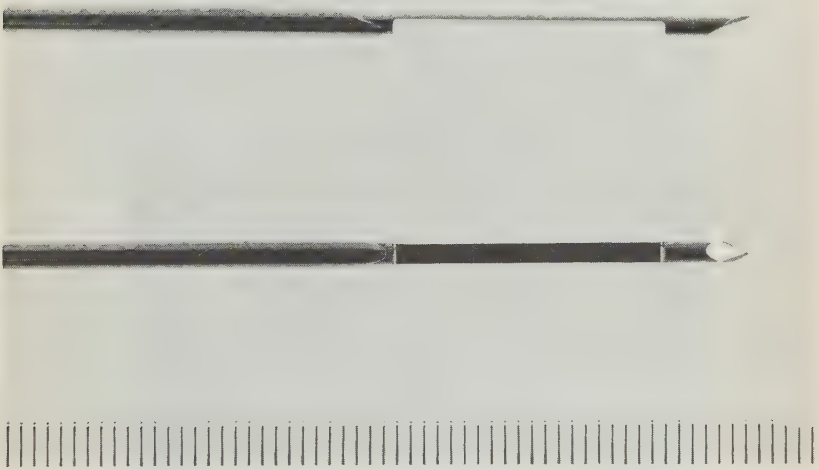

Figure 6. Closeup of Tru-Cut needle (mm scale).

THYROID DISEASES DIAGNOSED BY ABC

In our experience, the ABC technique permits diagnosis of the following thyroid lesions:

COLLOID GOITER. In colloid goiter the diagnosis is based upon the abundance of colloid with some often atrophic follicular cells (Fig. 7). In cystic colloid goiters, phagocytes are a frequent finding.

THYROIDITIS. Thyroiditis is classified according to the predominant inflammatory cell type.

Acute thyroiditis is likely to occur when the inflammatory component is granulocytic. This diagnosis should be made with caution because of the extreme rarity of this condition.

Subacute thyroiditis (de Quervain) is recognized by the granulomatous character of the inflammatory changes, the presence of histiocytic giant cells, and degenerative changes of the glandular cells.

Chronic lymphocytic thyroiditis (Hashimoto's disease) is recognized by lymphocytes and follicular cells showing oncocytic changes.

NEOPLASMS. As a rule, neoplasms are identified by highly cellular smears with tumor patterns.

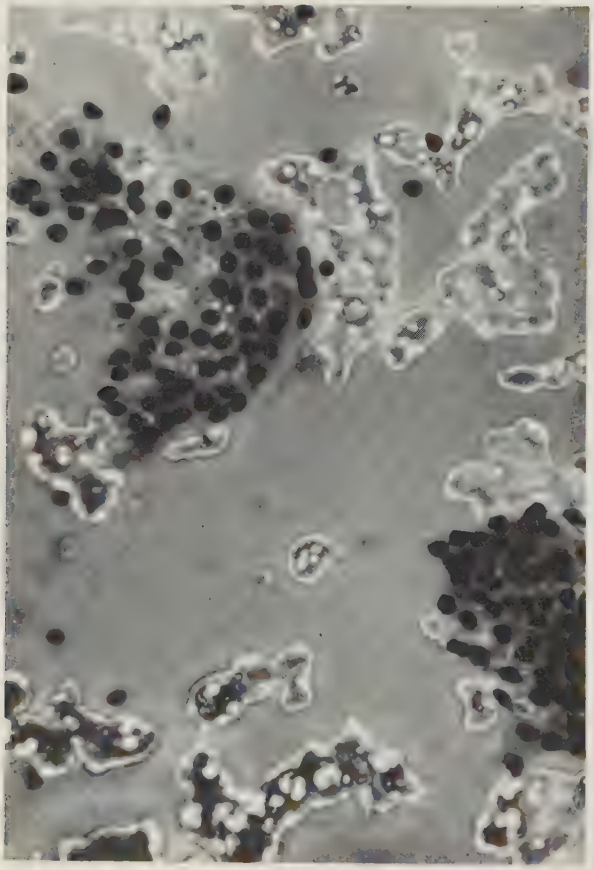

Figure 7. Colloid goiter: colloid background and a few small follicular cells.

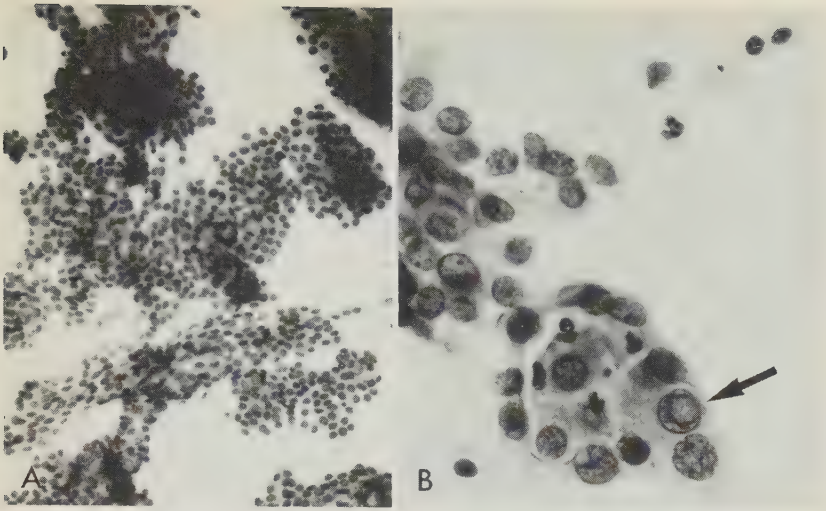

Figure 8. Papillary cancer. *A*, Equi-sized circular clusters in a papillary pattern. *B*, Higher magnification reveals pseudonucleoli.

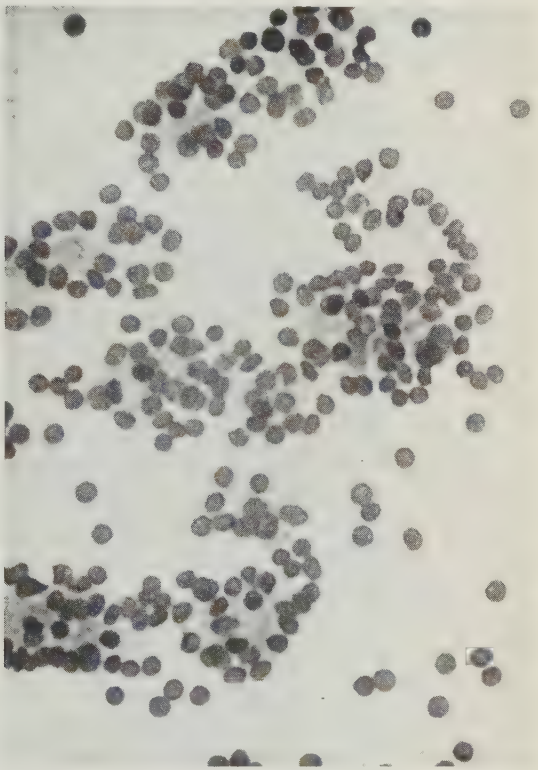

Figure 9. Follicular tumors: equi-sized circular clusters.

Papillary cancer is recognized by the papillary form of the tumor fragments (Fig. 8*A*). Particularly helpful for diagnosis is the presence of pseudonucleoli (intranuclear cytoplasmic inclusions) (Fig. 8*B*).[12]

Follicular tumors are characterized by monotonously repeated microfollicular cell clusters (Fig. 9). ABC *cannot* confidently distinguish

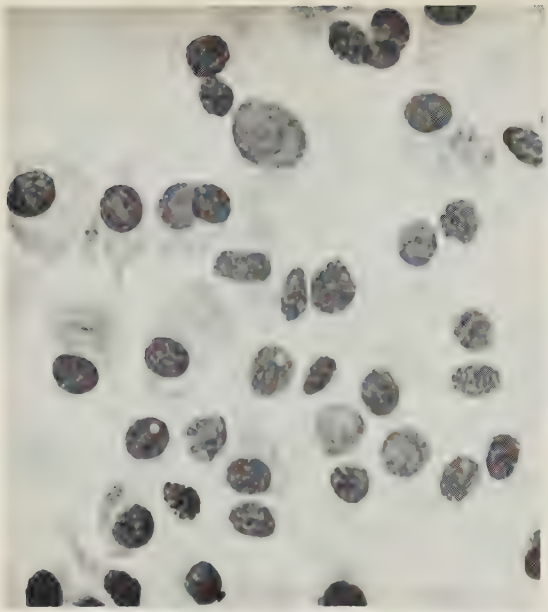

Figure 10. Medullary cancer: dispersed cell pattern, tail-like cytoplasmic projections, cytoplasmic granuli, and variable nuclear size.

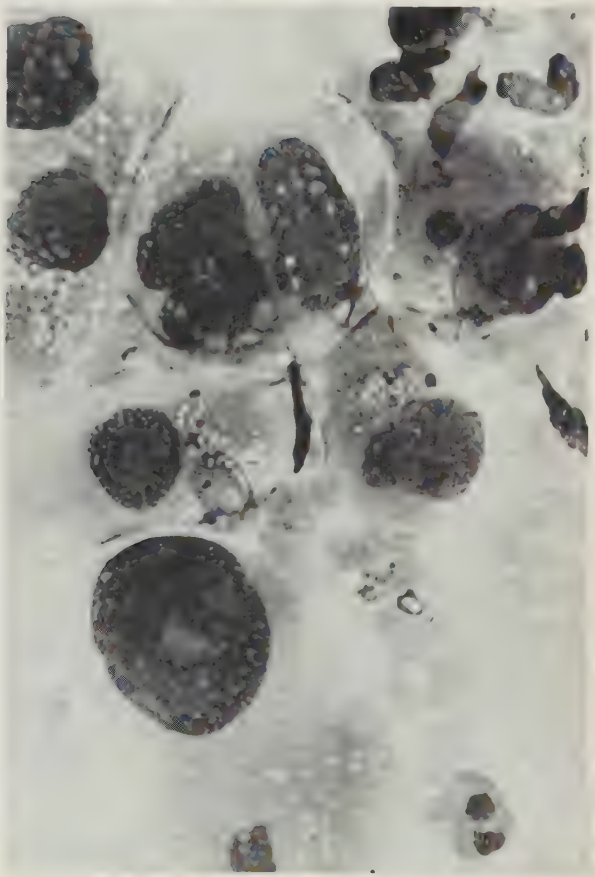

Figure 11. Anaplastic giant cell cancer: large polymorphic binucleated cells.

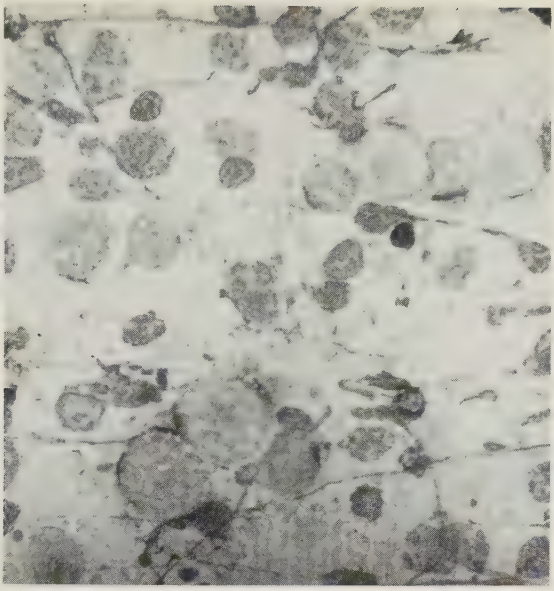

Figure 12. Small cell anaplastic tumor: undifferentiated cells in a lymphomatous pattern.

between a follicular adenoma and a follicular carcinoma,[19] as often only multiple sections of the capsule will show an invasive pattern.

Medullary cancer displays a typical dispersed cell pattern. The cells tend to be elongated and the cytoplasm is often granular. Amyloid is a common finding (Fig. 10).

Anaplastic carcinomas exhibit the most malignant cell pattern. The *giant cell type* presents as heterogeneous material composed of necrotic tissue mixed with bizarre giant cells (Fig. 11), whereas the *small cell type* exhibits a cell pattern consistent with that of a lymphoma (Fig. 12).

CLINICAL EXPERIENCE

To evaluate the accuracy of ABC in the diagnosis of malignant thyroid tumors, we have studied patients treated surgically at this hospital. All patients who underwent a primary operation for thyroid lesions suspected to be malignant, from 1970 to 1975 inclusive, and all patients in whom thyroid ABC had been performed preoperatively, were included in the study—a total of 412 patients. No patients with a cytologic diagnosis of thyroiditis underwent operation during that period.

Patients were selected on the basis of history, physical findings, thyroid scintigraphy (^{131}I or ^{99m}Tc-pertechnetate) and fine needle aspiration biopsy of lesions suspected to be malignant. Surgery was performed in all patients with a decreased accumulation of radionuclide in a palpable thyroid nodule regardless of the ABC findings, and in those whose cytologic examinations showed malignancy or suspected malignancy.

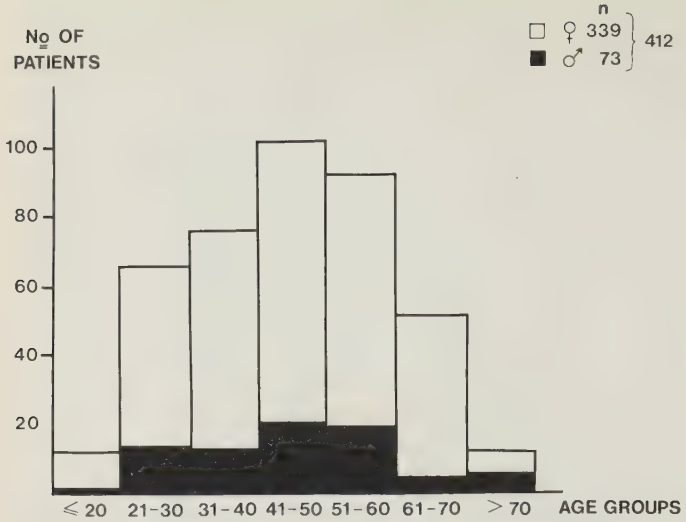

Figure 13. Age and sex distribution of patients who presented with thyroid lesions (see text for details). Note the predominance of women (82 per cent).

For all cases in this study the original reports of ABC, scintigraphy and histopathology were used. The age distribution of the 73 male and 339 female patients is given in Figure 13. Preoperative scintigraphy was performed in 373 patients. Nine patients gave a history of previous radiation therapy to the neck region.

Thyroid Scintigraphy

^{99m}Tc-pertechnetate was used in all patients below the age of 40 years in whom the clinical suspicion of malignancy was not considered to be high. In all other patients, ^{131}I was utilized. One mCi of ^{99m}Tc was given intravenously or orally one half to one hour before the scanning procedure or, in the case of ^{131}I, 60 μCi was given orally 24 hours before scintigraphy. The recording apparatus was a Picker Magna Scanner equipped with a focusing collimator and a crystal three inches in diameter. The result of the thyroid scintigraphy was compared with the palpation findings with the patient in the same position as during the scintigraphic procedure.

Surgical Procedure

Following outpatient scintiscan and ABC examinations, all patients were admitted for operation. The extent of the surgical procedure was determined by the cytologic diagnosis and the findings during operation. The three operative procedures used most frequently are described below.

Bilateral or unilateral subtotal thyroid lobectomy was used in all patients in whom, during surgery, nontoxic nodular goiters were found, in accordance with the ABC findings.

Hemithyroidectomy was employed in all patients with a unilateral solitary nodule, most being follicular adenomas. If the permanent histopathologic examination revealed a malignant tumor, hemithyroidectomy of the remaining lobe was done within two to four days.

Total thyroidectomy was carried out in all patients with papillary or medullary carcinomas and was extended to a modified neck dissection in patients with metastatic spread of tumor to the regional lymph glands.

Histopathologic Examinations

All operative specimens were histopathologically examined by pathologists who did not have previous knowledge of the ABC diagnosis. The classification was made in accordance with the system presented by the World Health Organization.[10]

RESULTS

The result of the preoperative ABC findings in comparison with the final histopathology is shown in Figure 14. The preoperative ABC diagnosis showed malignant tumors in 63, tumors suspected to be malignant in 123, and benign disorders in 226 patients. The definite diagnosis from the histopathologic examination was thyroid cancer in 96 (23.3 per cent), benign tumors in 163 (39.6 per cent), and benign goiter in 153 patients (37.1 per cent).

ABC gave no false positive results as regards malignancy (Fig. 14 and Table 1). False negative results, i.e., patients in whom the cytologic diagnosis was judged primarily to be benign, but was found later to be malignant by histopathologic examination, occurred in 9 of 412 patients (2.2 per cent). The ABC diagnosis gave a suspicion of malignancy in 123 patients, representing almost all of the follicular tumors that thus were not clas-

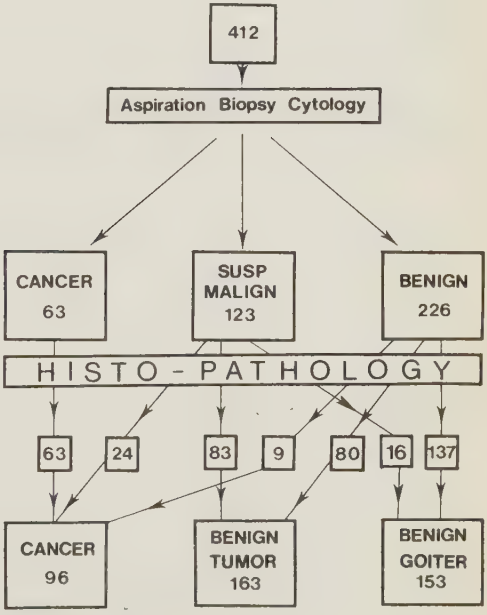

Figure 14. Accuracy of diagnosis by ABC as compared with definite histopathologic diagnosis.

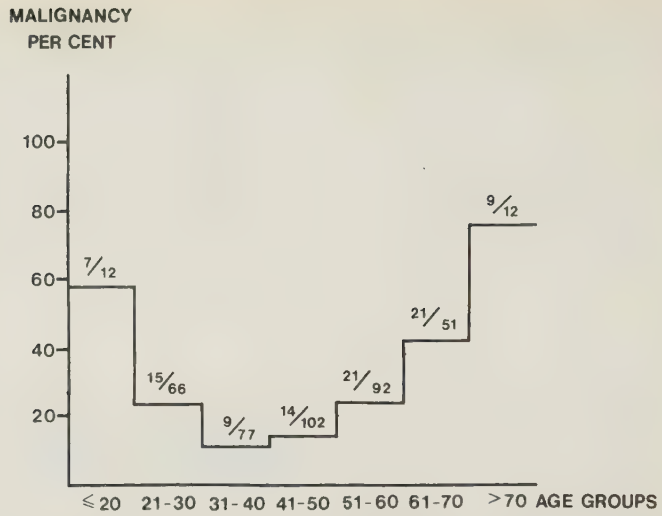

Figure 15. Distribution of malignancy rate in different age groups. Ratio figures express the number of patients with a definite diagnosis of malignant tumor/total number of patients in respective age groups.

sified as false negatives. As pointed out earlier, histopathologic investigations of the capsule are necessary to establish a diagnosis of follicular carcinoma.

The percentage age distribution of the patients with histopathologically verified malignant tumors is given in Figure 15. The highest incidence of malignant tumors was found in the youngest and oldest age groups.

Radionuclide Investigations

Thyroid scintigraphy was performed in all but 39 patients. Table 2 shows the distribution of patients with respect to scan and tissue pathology. Decreased radionuclide accumulation (^{131}I or ^{99m}Tc-pertechnetate)

Table 1. *False Diagnosis by ABC in Tumors of the Thyroid Suspected to be Malignant*

YEAR	NO. OF PATIENTS	FALSE POSITIVE* (PER CENT)	FALSE NEGATIVE* (PER CENT)
1970	64	0	5.0
1971	64	0	7.2
1972	73	0	1.4
1973	84	0	0
1974	74	0	0
1975	53	0	0
TOTAL	412	0	2.2

*For follicular tumors, see text.

Table 2. *Thyroid Scintigraphy in Tumors of the Thyroid Suspected to be Malignant*

APPEARANCE ON SCAN	NO. OF PATIENTS	HISTOPATHOLOGY Malignant Tumor	Benign Tumor	Benign Goiter
Decreased	375	76	147	134
Not conclusive	16	2	5	9
Not investigated	39	18	11	10

was found in all histopathologic groups. No difference was observed between the two radionuclides in this respect. In the group with malignant tumors, a "cold nodule" was observed in 76 of the 78 patients examined (97 per cent).

Figure 16 shows the percentage age distribution of cancer, benign tumor, and benign goiter in patients exhibiting a decreased radionuclide accumulation in a palpable thyroid lesion (357 patients). No benign goiters were found in patients below the age of 21 years and no benign tumors were observed in patients above the age of 70 years. Thus, the percentage incidence of malignant tumors is highest in the youngest and oldest age groups.

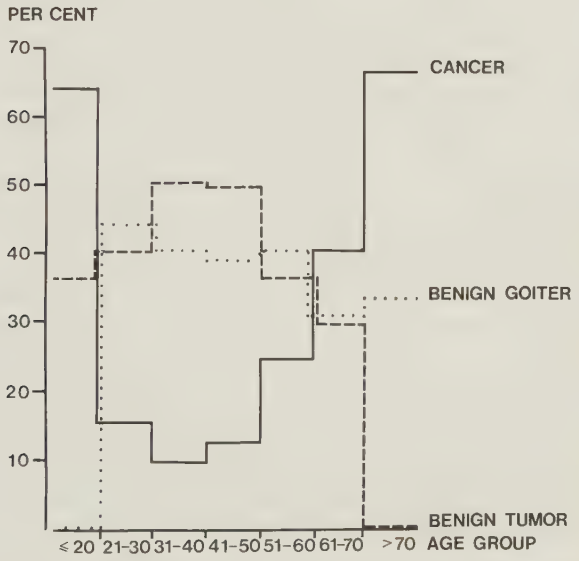

Figure 16. Percentage age distribution of cancer, benign tumor, and benign goiter in 357 patients with decreased radionuclide accumulation in a palpable lesion.

DISCUSSION

From our data it is evident that diagnosis by fine needle aspiration biopsy cytology of the thyroid gland makes possible selection of patients for surgery with a high degree of accuracy when there is a question of whether palpable thyroid nodules are benign or malignant.

We have used the ABC technique for more than 20 years and it is an accurate tool in diagnosing malignant and inflammatory disorders of the thyroid gland. ABC is often the only procedure necessary to obtain an accurate diagnosis.

The investigations are often combined with scintigraphy of the thyroid gland. These methods together increase the accuracy of the preoperative diagnosis. In our series of patients a preliminary screening was made by thyroid scintigraphy, which identified for cytologists the areas suspected to be affected by malignant tumors, whether or not they were palpable. In our investigation, only 3 per cent of the scintigraphically examined carcinomas did not exhibit a clearly decreased accumulation of radionuclide. Thus, the risk of misjudging a carcinoma of the thyroid is low when ABC and scintigraphy are combined.

In our investigations no false positive cytologic results of malignancy were observed. This obviously is of great importance in planning the management of the patient with a tumor suspected to be malignant: We regard an ABC diagnosis of malignant tumors to be certain and do not await permanent histopathologic results before the definitive operation is performed.

The results of the present study have strengthened our confidence in ABC in planning the definite operation. If ABC reveals a papillary or medullary tumor pattern, we consider the tumor to be malignant and perform total thyroidectomy. As ABC cannot differentiate between a follicular adenoma and a follicular cancer, a hemithyroidectomy with histologic examination of the excised tumor is required.

In the ABC diagnosis of tumors, 5 to 10 per cent are false negative findings.[8, 17, 18, 19] Our false negative findings were 2.2 per cent, and no false negatives were observed during the last three years of the observation period. We believe that the teamwork that is applied at our hospital might contribute to the results obtained. Of paramount importance is, however, the cytopathologist in our team.

Esselstyn and Crile[6] claim that the surgeon who evaluates the goiter should perform the puncture. In a study from southern Sweden[1] ABC was found to be 25 per cent less accurate when surgeons performed the aspiration than when it was performed by trained cytopathologists. Inadequate aspiration, failure in producing acceptable smears, or faulty fixation were reasons for this difference. Even if many of these figures can be improved by training, it is our opinion that the best results are gained when a specially trained cytopathologist examines the patient, performs the aspiration, makes the smear, and reads the slides. A similar view is also expressed by some American pathologists.[8]

Esselstyn and Crile[6] do not differentiate between the technique of needle biopsy whether it be Vim-Silverman or Tru-Cut or ABC. Since ABC is based on a different principle than that of large bore needles, we think it is important to separate the two methods. Whereas in ABC a smear is enough, with big needles a piece of the tissue has to be cut from the parenchyma. ABC is easier to perform, can be easily repeated with the patient's acceptance, and is free from complications. We believe that the ABC method of biopsy is superior to the conventional large bore technique by virtue of: less likelihood of insufficient material, less soreness and bleeding, and an almost negligible risk of hoarseness from recurrent nerve injury.

Esselstyn and Crile[6] present a procedure with aspiration cytology that is different from the one we use. They flush the aspirate into Zenker's solution and make a block of the sediment. This method is more time-consuming and less preferable than the direct staining of the smear, as is our routine.

This study was made to obtain data on the accuracy of fine needle aspiration biopsy of thyroid lesions. The results confirm our impression that ABC is a method allowing a very high degree of diagnostic accuracy.

We endorse Frable's[8] comment that it seems ironic to spend unnecessary sums for biochemical, angiographic, ultrasonic, and radionuclide tests to determine the nature of a lump in the thyroid, when with ABC the diagnosis in most cases can be established in minutes.

ABC avoids unnecessary operations. Undifferentiated carcinomas of the thyroid should, according to our experience, not be operated upon immediately. Giant cell anaplastic carcinoma is preoperatively treated with radiation in combination with chemotherapy. For undifferentiated small cell carcinomas, only radiation and chemotherapy are the treatments of choice. If ABC is consistent with a nontoxic nodular goiter or inflammatory diseases, the patient is not operated upon. These patients are followed with sequential ABC biopsy if necessary.

In the material presented, no patient with cancer had previously undergone ABC with a diagnosis of benign tumor.

ABC must be used with caution in cysts in the thyroid gland and lymph nodes. Many cysts occur in malignancies.[1, 4, 8] While cytology is performed on the aspirated fluid, it is even more important to check for a residual mass after emptying the cyst and then repeat the ABC as necessary. The finding of cyst fluid outside of the thyroid region is suspicious for a nodal metastasis of thyroid carcinoma.

CONCLUSIONS

ABC is a safe and accurate method for establishing whether a thyroid nodule is benign or malignant. Diagnostic operations are avoided in many patients.

ABC has to be differentiated from needle biopsy with Vim-Silverman or Tru-Cut needles, as the methods embody different principles.

ABC does not cause complications, and it has patient acceptance. ABC requires no anesthesia.

ABC cannot differentiate a follicular adenoma from a follicular carcinoma. In such cases the final diagnosis depends on histologic examination of the excised tumor.

While there is no need to hesitate in repeating an ABC, one should still proceed with surgical exploration when there is a clinical suspicion of malignancy despite a negative cytologic diagnosis.

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The Ultrasound of Thyroid Masses

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It has been estimated that about 5 per cent of the adult population in North America bears the stigma of goiter, and selection of patients for operative treatment is still an ongoing problem that commands the attention of physicians and surgeons interested in thyroid disease. Ultrasonography has been applied in the diagnosis of problems throughout the body and has been used to scrutinize thyroid lesions as well. While its place in diagnostic approach has not been defined, it represents the first modality that has established the physical state of the thyroid lesion on a clinical basis alone.

Ultrasonic Principles

The ultrasonic beam is made up of high frequency sound waves greater than 1 million cycles per second and therefore much beyond the range of human hearing. Such a beam mimics a light beam in that it can be focused, reflected, refracted, and, depending on the medium of transmission, attenuated. Acoustic impedance is that property of biological material which is responsible for reflection and is the product of the density of the medium and wave velocity. Wave velocity does not vary much among liquids despite differences in density. Transmission of sound in most biological material with the exception of bone is similar to that in liquids. The amount of sound reflected at interphases depends on the magnitude of the difference in acoustic impedance. Sonic beams are almost totally reflected at air tissue levels necessitating the application of solutions and creams to patients' skin to avoid total reflection. It is not

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possible to scan biological targets that contain air, such as the lungs, and it is difficult if not impossible to obtain echoes from the far side of bone. The average power levels used in diagnostic ultrasound are several orders of magnitude below the levels quoted as producing tissue damage. In the thyroid gland there is no significant reflection of sound waves during their transmission through cystic lesions, as compared with solid lesions in which echoes are produced by contained multilayered interphases. This phenomenon is basic to the understanding of thyroid ultrasonography.[2]

Ultrasonographic Technology and Terms

The transducer is a device that converts electric to ultrasonic energy and is made up of piezoelectric materials such as quartz. A brief electrical signal excites the piezoelectric material which then undergoes periodic changes in thickness, setting up periodic waves of compression and rarefaction (sound waves) which are transmitted to the patient. The transducer relaxes to its resting thickness to await the return of an echo which in turn causes it to generate electrical signals. The speed of the sound waves and the time lapse between sent and received signals permit one to determine the distance to the target. Focused and nonfocused transducers range from 2.25 to 10.0 MHz, with the higher frequency giving better resolution but shorter penetration. Sound energy is converted to electric energy and light energy which is usually displayed on an oscilloscope cathode ray tube after suitable amplification. Permanent records can be made by means of Polaroid or 8 by 10 x-ray films. Bistable equipment records images in black and white. Recent improvements by use of television monitors and scan converters have permitted gray scale images which permit gradation of images from black to white with shades of gray between. An A-mode presentation depicts an ultrasonic signal in a unidirectional way as a line on an oscilloscope. The stronger the echo signal, the higher the spike on the oscilloscope. The horizontal distance between two spikes is a measure of the distance between interphases. In B-scan ultrasound the transducer is attached to a movable arm so that a sonar laminogram or cross-section can be displayed as a bright dot on a storage type oscilloscope and recorded. Sonolucence refers to the absence of echoes or reflected ultrasound waves seen characteristically in cystic lesions. Sensitivity or gain refers to the amplification capability of a system including the transducer in electronics. Higher gains may produce echoes not previously detected in bistable machines.[4]

Ultrasonographic Examination of the Thyroid Gland

The patient is placed in a supine position on a stretcher with a cushion beneath the upper back to permit cervical extension (Fig. 1). Vegetable oil is applied to the neck to provide an economic and effective couplant. In performing B-scans, the examiner stands on the right-hand side of the patient and uses his right hand to guide a transducer across the patient's neck. If the transducer is held by thumb and index finger, the middle finger can be kept in contact with the patient's skin to guide the examiner's hand in a smooth passage across the neck while he concentrates on the image being built up on the television screen. This permits the produc-

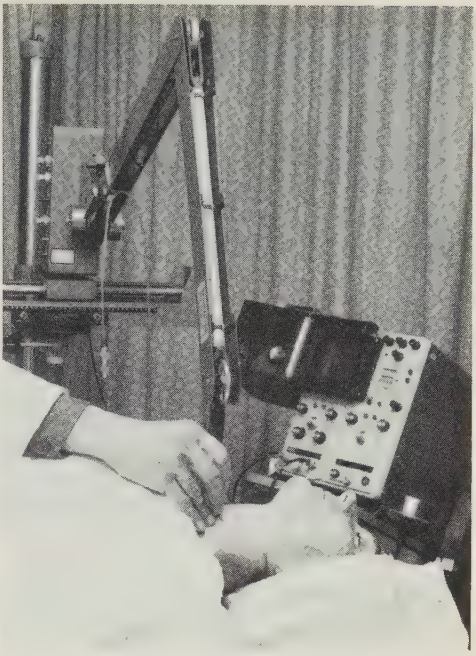

Figure 1. Thyroid ultrasound examination. The examiner stands at the patient's right with the transducer in his hand against the patient's extended neck which is coated with vegetable oil and usually makes transverse passes across the neck at varying levels above the sternal notch. Echoes are registered on the screen as an image and printed for permanent record on polaroid or x-ray film.

tion of neat reproducible sonograms. The suprasternal notch is used as a baseline and serial transverse sonograms are made at 1 or 0.5 cm intervals beginning at the notch and passing cranialward until the entire gland appears to be completely studied. Sonograms are made both at low and high gain or sensitivity settings, particularly at points of interest or where differentiation between solid and cystic lesions is necessary (Figs. 2 and 3). When the thyroid mass has been adequately assessed by B-scanning technique, it can be further assessed with A-scan. In this technique, the transducer is placed over the center of the lesion and the sensitivity is sequentially increased to assess the appearance of internal echoes. If the ultrasound equipment has simultaneous A-mode and B-mode displays,

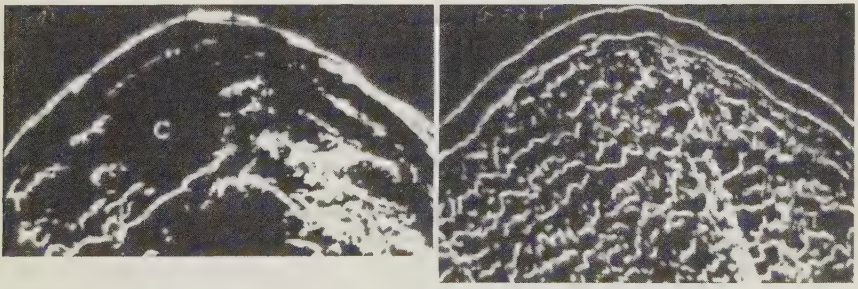

Figure 2. Bistable transverse sonogram shows a solid cancer (C) to be sonolucent at low sensitivity of 2.0 (left) and fills in with echoes (right) as sensitivity is increased. Cystic lesion would not fill in with echoes despite increase in sensitivity.

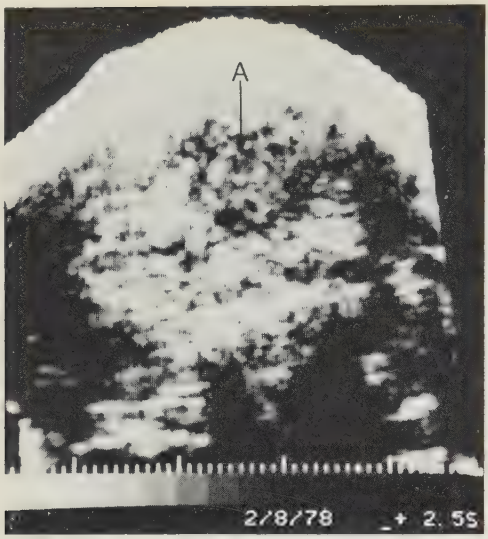

Figure 3. Gray scale sonogram of a solid adenoma (A) shows contrast to the bistable image that it has largely replaced. Echoes are always present in solid lesions although increase in sensitivity increases their number and definition.

then one screen scope may be kept on B-mode to ensure accurate aiming of the transducer through the center of the lesion while developing an echo pattern in the A-mode of the screen. Permanent records are established by Polaroid photographs or preferably 8 by 10 x-ray films which are more economical. We prefer the compound contact scanner (Picker ultrasonoscope) with a 5 MHz transducer. When very large glands are encountered requiring deeper penetration, a 2.5 MHz transducer has been employed. Sensitivity settings range from low (2.2 on equipment used) through intermediate (2.5) and high (3.0), to very high (3.5). B-mode ultrasonography with the gray scale method is now used exclusively at our institution for examination of the thyroid gland.[5]

Normal Ultrasonic Anatomy of the Thyroid Gland

The B-mode ultrasonogram in a normal patient without disease of the thyroid gland can show a variety of structures although the gland is not pre-eminent (Fig. 4). One can detect a linear uniform line of reflected echoes comprising the skin and presumably the superficial cervical fascia as indicated on the diagram. The thyroid gland is represented by a paratracheal scattering of fine echoes which are scanty in the normal unenlarged thyroid gland. The anterior surface of the trachea can be seen but the entire lumen or cross-section of the trachea cannot be echo demonstrated since echoes cannot traverse the air filled lumen of trachea. The carotid sheath containing carotid artery and internal jugular vein can be seen as cross-sectional sonolucent holes. While vascular abnormalities are not pertinent to this paper, it should be noted that authors have described the sonographic discernment of carotid atherosclerosis, aneurysms, and chemodectomas, and believe that ultrasonography can be effective in discriminating between transmitted and true pulsatility in cervical masses.[9] Sternomastoid muscles are laterally placed and are

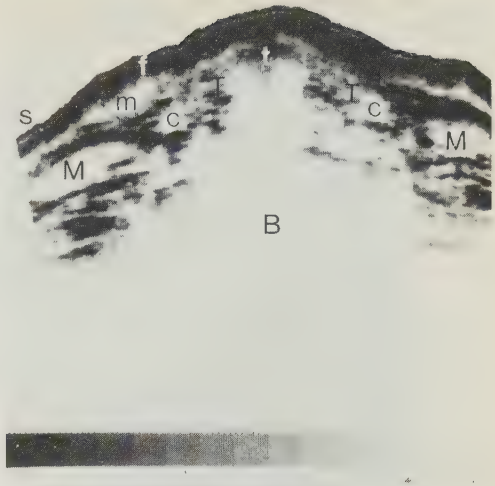

Figure 4. Normal transverse neck anatomy showing skin (S), superficial fascia (f), trachea (t), carotid sheath (c), strap muscle (m), sternomastoid muscle (M), thyroid (T), and cervical vertebrae (B). Note scale marked off in millimeters which permits direct measurement of any lesion.

composed of irregular areas filled with low-level echoes that appear to have discrete anterior and posterior borders corresponding to the surfaces of the muscle. The cervical spines are a u-shaped anechoic area in the sonogram since bone does not transmit ultrasound. While the inexperienced observer may find the normal sonogram to demand much imagination, the experienced echographer has little problem in correlating echo and normal anatomy.[5, 6]

Ultrasound of Cystic Thyroid Masses

Cystic lesions on B-mode scanning appear sonolucent at a low-gain setting and persist as sonolucent as the sensitivity is increased (Fig. 5).

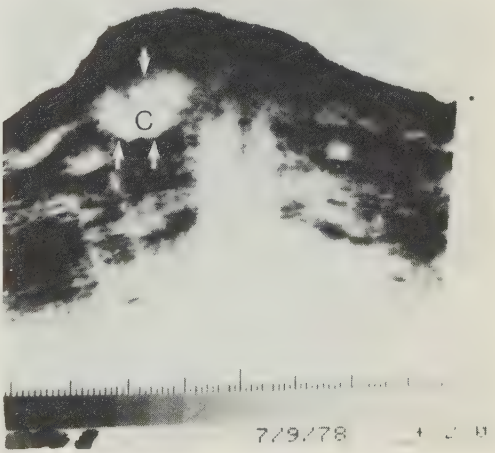

Figure 5. Thyroid cyst (C) is anechoic in its center and has a discrete posterior wall (↑↑) and anterior wall (↓).

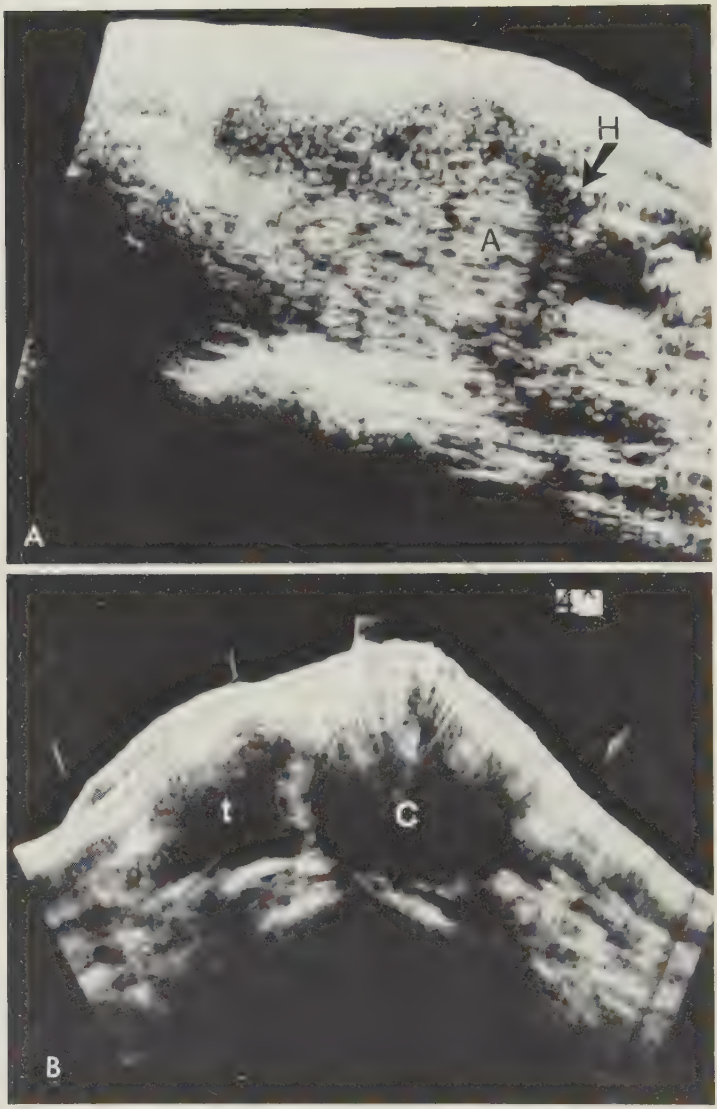

Figure 6. *A*, Longitudinal view of a thyroid adenoma (A) full of echoes and surrounded by "halo" (H) thought to be characteristic of benign disease. *B*, Transverse sonogram of a patient with solid left-sided thyroid cancer (C) and associated right-sided solid thyroiditis (th). Scanty echoes present bilaterally do not in any way distinguish histology.

There is a thin discrete posterior and anterior wall to the cyst since the wall of a cyst offers significant acoustic impedance differences between the cyst and surrounding tissue, yielding echo formation. An A-mode scan shows two spikes corresponding to the anterior and posterior wall of the cyst. As the sensitivity is increased, the cystic lesions will fill in slightly with echoes at the periphery. The dimensions of the cyst of course can be measured and its response to aspiration can be visualized and followed in an objective manner.[5, 6, 8]

Ultrasound of Solid Thyroid Masses

On B-mode ultrasonography and using a bistable scan, the solid thyroid tumor may be relatively sonolucent at a low-gain setting. As the sensitivity is increased to intermediate or high-gain settings, echoes become more obvious within the lesion, eventually filling it in. No discrete walls such as those found in cysts appear at higher gain settings. With the gray scale scan, this evolution is not seen. Echo formation is apparent as a feature of the solid lesion. Indeed, a lightening of relative decrease of echoes about a lesion is called the "halo" effect and has been cited as a characteristic of adenoma although this has not as yet been confirmed (Fig. 6*A*). Increasing amplitude in the gray scale defines and increases echoes but does not witness a change in their occurrence and distribution. In the A-mode examination, spikes are seen diagrammatically corresponding to echo formation occurring at the interphase between tumor and thyroid gland. Between these spikes are further multiple and smaller spike elevations, again indicative of echo formation occurring at the multiple soft tissue interphases that occur within the solid thyroid lesion. Nothing in the distribution, density, brightness, relationship to gain setting of echo formation, or its graphic depiction permits one to discriminate histologically between types of solid lesions. From an ultrasonographic point of view, solid adenomas, carcinomas, and colloid nodules are identical in appearance (Fig. 6*B*). Direct measurements can be made by echogram and can provide an objective basis for the measurement of response of a solid lesion to thyroid feeding.[5, 6, 8]

Ultrasound of Mixed Thyroid Masses

There is a small group of lesions which will display the characteristics of both solid and cystic lesions ultrasonographically. This is a group of solid lesions that have undergone cystic degeneration of varying degree (Fig. 7 and 8). Indeed, with gray scale scanning, the ability to detect a small sonolucent area is so great that many presumably solid lesions will show tiny clear areas, suggestive either of areas of fine cystic degeneration or perhaps vascularity. In contrast, in the bistable scan, the mixed lesion appears initially sonolucent at a low-gain setting, and, as the sensitivity is increased to intermediate or high-gain settings, the lesion fills in with echoes but not completely, leaving a persistent sonolucent area. Such cystic degeneration can be seen in carcinomas, adenomas, or colloid nodules, and it may be that every cyst in reality represents a degenerative stage of a solid lesion.[1]

Figure 7. Transverse view of adenoma (CA) with extensive cystic degeneration—a mixed lesion. Echogram shows infrequent echoes between predominant anechoic areas.

Figure 8. Longitudinal view of a mixed lesion that shows a relatively small area of cystic degeneration in a solid adenoma.

Ultrasound of Diffuse Thyroid Lesions

Nontoxic goiter, thyroiditis, and diffuse colloid goiter all represent a diffuse enlargement of the thyroid gland with a diffuse goiter of varying nodularity (Figs. 9 and 10). In the bistable B-mode scan at a low-gain setting, these lesions would give rise to a diffuse sonolucent area demarcated from adjacent soft tissue of the neck, particularly sternomastoid muscle. As the gain setting is increased, this area would fill in with echoes in a rather patchy fashion. In a gray scale, the thyroid area is seen again to

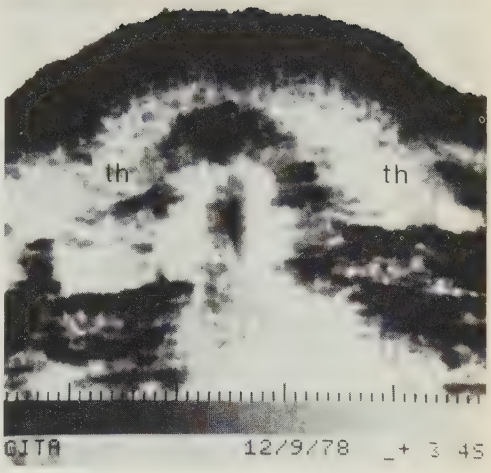

Figure 9. Transverse view of patient with subacute thyroiditis showing diffuse goiter (th) throughout the neck with some sparse echoes giving a pseudocystic echographic appearance.

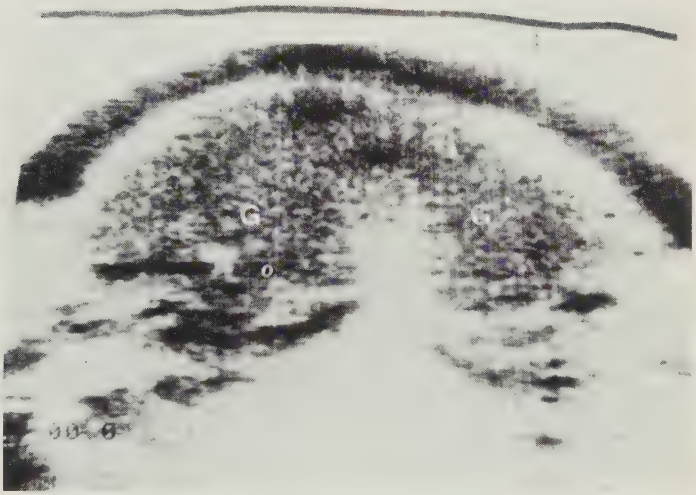

Figure 10. Transverse view of multinodular goiter (G) extending throughout neck and showing many relatively dense echoes.

show a thinner distribution of echo formation but distributed in a manner conforming to a diffusely enlarged thyroid gland. In thyroiditis, the distribution of echoes has on occasion been so patchy with sufficient sonolucent areas between them that a "pseudocystic" appearance has been described. This presumably would be accounted for by the edema and lymphoid infiltrate seen in thyroiditis. This, however, may be seen in nontoxic multinodular goiters as well. While this appearance is of interest, it is not characteristic and should not be utilized as an absolute discriminant of underlying histology.[5, 6, 8]

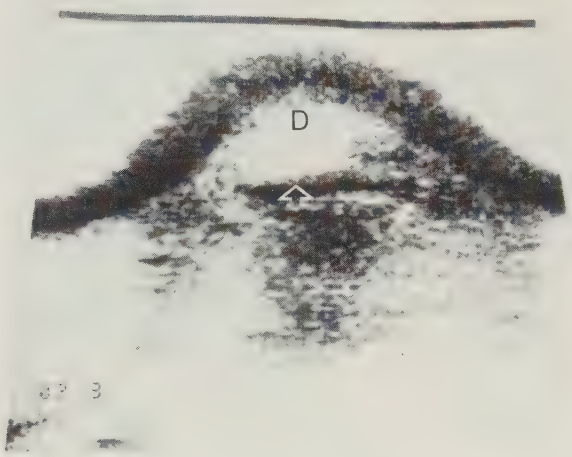

Figure 11. Transverse view of thyroglossal duct cyst (D) at subhyoid position showing sonolucent center and discrete posterior wall (↑).

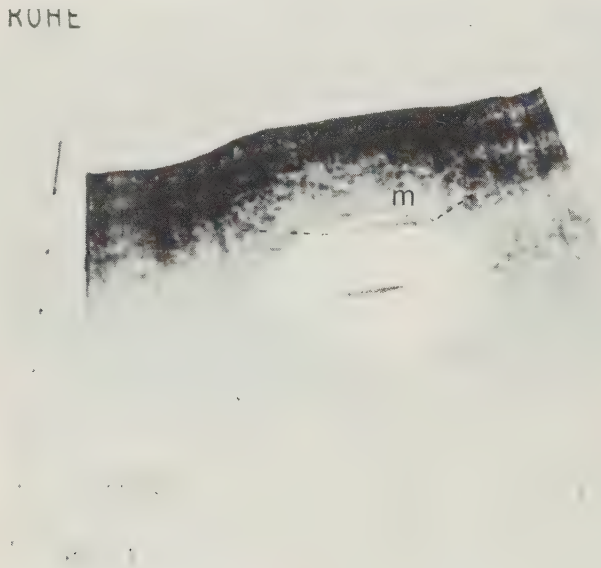

Figure 12. Longitudinal view of a subhyoid ectopic thyroid gland that had undergone malignant degeneration (M). In contrast to the thyroglossal duct cyst, this lesion is full of echoes.

Ultrasound of Thyroid Associated Masses

Ultrasonography can also be utilized to assess lesions associated with the thyroid gland, either geographically such as midline dermoid cysts of the neck, or developmentally such as thyroglossal duct cysts (Fig. 11). Both of these lesions would of course demonstrate the classic echographic parameters of a cystic lesion. The echogram then permits one to discriminate the rare ectopic subhyoid thyroid (Fig. 12) and its attendant increased incidence of malignant degeneration from the much commoner thyroglossal duct cyst.[7]

Assessment of Thyroid Disease by Ultrasonography

We recently reported on more than 500 patients with goiter who have undergone thyroid ultrasonography. Within this group, 174 underwent pathological verification, usually by partial thyroidectomy and whole specimen pathological examination.[5] A comparison of the echographic preoperative diagnoses in tissue findings was then carried out. In 29 cancers, echography detected 26 to be solid, one cystic, and two mixed, whereas tissue findings showed 26 solid, none cystic, and three mixed. In 69 cases of adenoma, 68 were solid and one mixed, showing complete echographic correlation. Adenoma with cystic degeneration occurred in 13 patients, and in two of these, echography indicated a solid lesion, and in three a cyst. Colloid nodules were found to be solid in 16 cases and cystic in one, whereas echography revealed a complete cyst in one case. In 25 cases of cyst formation, three were thought to be solid by echography. In seven cases of thyroiditis, there was perfect correlation, as there was in 11 cases of goiter and three cases of goiter with cyst formation. Seven errors were made in the ultrasonographic assessment of the physical character of the thyroid lesion in 174 cases, giving an accuracy rate of 96 per cent (Table 1).

Nodules less than 1 cm are difficult to assess by ultrasonography although the advent of gray scale ultrasound makes this less of a problem. If the nodule is flat and broad, its definition can be a problem, and, on occasion, bulging nodules may prevent the proper application of the transducer which then interferes with the transmission and reception of

Table 1. *Validity of Preoperative Thyroid Ultrasound in 174 Patients*

DISEASE	NUMBER OF PATIENTS	ECHOGRAPHIC DIAGNOSIS			TISSUE FINDINGS		
		Cyst	Solid	Mixed	Cyst	Solid	Mixed
Cancer	29	1	26	2	0	26	3
Adenoma	69	0	68	1	0	68	1
Cyst adenoma	13	3	2	8	0	0	13
Colloid nodule	17	1	16	0	0	16	1
Cyst	25	22	0	3	25	0	0
Thyroiditis	7	0	7	0	0	7	0
Goiter	11	0	11	0	0	11	0
Goiter and cyst	31	3	0	0	3	0	0

ultrasound and its echoes. In order to circumvent this problem, a water bath technique has been used in which the part to be examined is isolated and the transducer is immersed in a water bath and does not contact the skin.[5, 7] This is particularly useful in the orbit but is otherwise awkward and subject to accidental leakage. Cystic lesions may show echo formations on echography. This paradoxical finding is explained by the occurrence of intracystic loculations or hemorrhage into a cyst with the formation of a hematoma. Echographic "mixed" lesions which show the combined features of a cyst and a solid tumor in a single lesion may on occasion be misdiagnosed by ultrasound. This depends on the extent of the cystic change. Thyroid lesions extending beneath the sternum cannot be properly assessed since ultrasound waves are totally reflected by bone so that no sound waves can penetrate.

The discrimination of cystic from solid lesions permitted us to select patients with echographic cysts for aspiration therapy and conservative management. As recommended by Crile[3] and generally accepted as reasonable practice, the fluid obtained was submitted for cytologic examination and the patients were re-examined in regular follow-up visits. This experience with needle aspiration encouraged us to carry out a prospective study on the validity of ultrasonography and fine needle aspiration cytology in the assessment and management of goiter.[10] One hundred and thirty-nine patients with solitary or dominant thyroid nodules found to be hypofunctioning on ^{131}I scintiscanning by Nuclear Chicago Pho-Dot equipment were selected for study since they were all considered to be at great risk for thyroid cancer and hence were candidates for operation. Definitive pathology was established by histologic examination of thyroidectomy specimens (Table 2). Adequate cytologic material was obtained from 93 per cent of patients, and overall cytologic accuracy was about 92.8 per cent.

There were 115 echographic solid lesions which made up 83 per cent of the series and which showed a 34 per cent incidence of malignant tumors (including Hürthle cell adenomas). The overall incidence of neoplasia including colloid nodules was 92 per cent. Cytologic accuracy was 91.4 per cent with false negative diagnoses seen in cytologic adenomas. Such "adenomas" were usually confirmed at rapid section but serial paraffin sectioning revealed the presence of capsular or vascular invasion, revealing its true malignant personality. There were 16 echographic cystic lesions making up 11.5 per cent of the series with a 13 per cent incidence of cancer. There were eight mixed lesions with a 25 per cent

Table 2. *Information Obtained by Ultrasonography and Needle Biopsy in 139 Patients*

ECHOGRAPHIC FINDINGS	NUMBER OF LESIONS	NEOPLASMS	MALIGNANCIES	FALSE NEGATIVE CYTOLOGIC FINDINGS
Solid	115	92%	34%	5.9%
Cystic	16	80%	13%	8.3%
Mixed	8	75%	25%	8.3%

incidence of cancer. False negative reports occurred in 8.3 per cent of cases.

Thyroid Ultrasonography in Clinical Practice

Ultrasonography's chief role in assessment of goiter is to distinguish nonoperatively between cystic and solid lesions. This is of great importance to the patient. Further, it has been estimated that up to 20 per cent of hypofunctioning solitary nodules may be cystic in nature. Crile[3] has long championed the view that is now generally held—that thyroid cysts are overwhelmingly benign and can be treated by needle aspiration, submission of fluid for cytology, clinical follow-up, and thyroid feeding. Some authors have pursued repeated aspirations and even the injection of sclerosants.[1] In general we hold with this conservative view. However, it must be strongly emphasized that thyroid cysts are not invariably benign. We have encountered a 13 per cent malignancy rate in our cyst population which represents a selected group and a 25 per cent cancer rate in our "mixed" group. The appearance of aspirated fluid may be helpful and can vary from crystal clear (consistent with parathyroid cyst), clear yellow transudate, chocolate-green turbid suggestive of degeneration, or frankly bloody which indicates a rapidly growing vascularized tumor. While aspiration and cytologic analysis of cyst fluid seem commendable in theory, it is difficult to detect malignant cells in cyst fluid, perhaps because they are infrequently shed or, more likely, are diluted by fluid. It is our practice to recommend operation to patients with cysts exceeding 4 cm, which recur after two aspirations (or promptly after one) or which fail to decompress after aspiration. Operation is also recommended to patients with an accompanying history of neck irradiation, with suspicious findings on cytology or bloody fluid. Differentiation of a bloody tap from actual blood may be difficult. Echography can permit the selection of an appropriate size of needle to avoid trauma and the production of a bloody tap. Thus if the ultrasonic picture is that of a cyst, then a No. 18 needle may be used, whereas a No. 21 can be used for solid lesions. Fine needle aspiration cytology has proved helpful and will change the practice of thyroidology.[1, 10] The cytologic demonstration of benign disease has permitted the safe institution of conservative management in patients with multinodularity, who are compromised by age, debility, or medical disorder, or who refuse operation. The unexpected cytologic finding of malignancy in an apparently benign lesion is obviously valuable and the demonstration of tumor cells can convince a reluctant patient of the need of operation.

Ultrasound permits the exact measurement of a thyroid lesion so that size can be objectively determined. This can be particularly useful for the patient undergoing thyroid feeding in an attempt to suppress TSH and reduce thyroid nodules. Echographic measurement is obviously superior to subjective assessment of thyroid size by clinical palpation and assessment, and permits a judgment of response to treatment since serial ultrasound examinations can be carried out. Similarly the effect of aspiration of thyroid cysts can be documented but this is usually dramatically demonstrable by clinical means.

Lack of ionizing radiation makes ultrasonography particularly useful in the examination of thyroid masses in children and pregnant women.

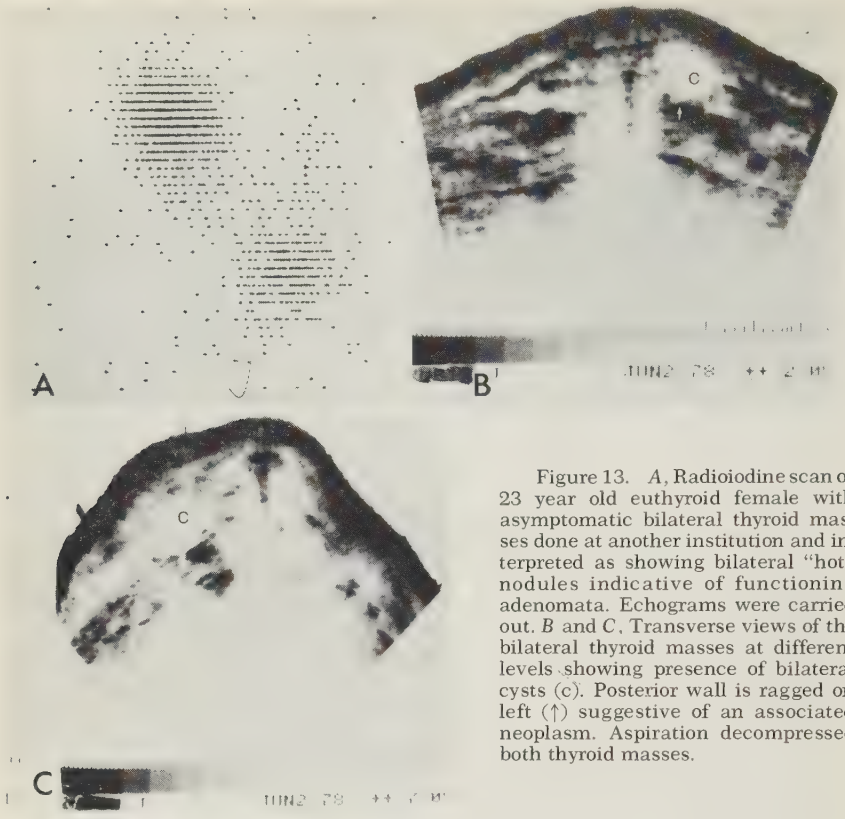

Figure 13. *A*, Radioiodine scan of 23 year old euthyroid female with asymptomatic bilateral thyroid masses done at another institution and interpreted as showing bilateral "hot" nodules indicative of functioning adenomata. Echograms were carried out. *B* and *C*, Transverse views of the bilateral thyroid masses at different levels showing presence of bilateral cysts (c). Posterior wall is ragged on left (↑) suggestive of an associated neoplasm. Aspiration decompressed both thyroid masses.

Following establishment of thyroid function studies, it is the investigation of choice in this group. Ultrasound creates no tissue injury at energy levels utilized in diagnostic work.[2, 4, 5] Thus ultrasound is a modality of thyroid investigation which is painless, harmless, noninvasive, and which can be repeated without fear of tissue injury. The application of ultrasound permits a complete picture of the patient with goiter and will complement the radioiodine scan. We have encountered a patient who had been followed for a year at another institution with what was presumed to be a hyperfunctioning adenoma (Fig. 13,*A* to *C*). Echography indicated this to be a cyst, and simple needle aspiration was effective, suggesting that the original scan interpretation may have been in error. Special thyroid clinics or referral centers will include ultrasound in their armamentarium of investigation. The use of ultrasonography has led to widening experience with fine needle aspiration cytology which appears to be of great significance in the clinical management of the patient with goiter. At present, the combined use of ultrasonography and fine needle aspiration cytology appears to be the most precise method of establishing preoperative diagnosis of thyroid tissue, permitting intelligent selection of treatment for the individual patient.

Summary

Ultrasonography of the thyroid gland permits differentiation between cystic, solid, and mixed lesions, allowing conservative management of cystic lesions, which constitute 20 per cent of hypofunctioning nodules. The combination of ultrasonography and fine needle aspiration cytology appears to be a great advance in the preoperative diagnosis of nontoxic goiter and permits individualized treatment in as precise a manner as is possible at present.

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Reemergence of Thyroidectomy as Treatment for Graves' Disease

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Subtotal thyroidectomy was the primary treatment for Graves' disease until the introduction of radioactive iodine in the 1940's. Thereafter, control of thyrotoxicosis with radioiodine became increasingly popular, to the extent that it is even used in the treatment of children with this disease by some respected clinics.[14] In recent years, however, the pendulum appears to be swinging back to thyroidectomy as the definitive treatment for this disorder. This trend is related to the recognition of the following factors: the incidence of hypothyroidism continues to increase with each passing year following treatment with radioactive iodine as it is usually administered; the margin of safety of thyroidectomy is now even greater because of the use of propranolol in the preoperative, intraoperative, and postoperative care of patients; and finally, of greatest importance, there is a greater perception by patients and physicians alike of the potential dangers of radiation therapy.

The purpose of this article is to discuss the advantages and disadvantages of the different forms of therapy for Graves' disease and to review the results of a group of patients treated by subtotal thyroidectomy at the University of Chicago Hospitals in recent years.

DIFFERENT TYPES OF THERAPY FOR THYROTOXICOSIS

Three forms of therapy are available for the treatment of thyrotoxicosis: blocking of thyroid hormone synthesis by antithyroid drugs, destruction of the thyroid by radioactive iodine therapy, and subtotal resection of the thyroid gland. Each has advantages and disadvantages.

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Antithyroid Drugs

Treatment of patients with diffuse toxic goiter with a thiocarbamide drug, such as propylthiouracil (PTU) and methimazole (Tapazole), is attractive since no operation is required, no harm is done to the parathyroid glands or to the recurrent laryngeal nerves, and no radiation exposure occurs. It is also one of the least expensive forms of therapy. However, it requires the patient to take her medication strictly every eight hours and to make frequent visits to a physician for reevaluation. We have found that many of our patients do not comply well with this program and have great difficulty in taking their medication and returning for clinic visits. In addition, toxic reactions to the drugs occur in 3 to 12 per cent of patients.[1, 24] Fever, rash, pruritus, arthralgias, jaundice, and polyserositis may occur. The most serious reactions are neutropenia and agranulocytosis. Furthermore, after taking medication for one year, only about one-third of individuals with Graves' disease will have a permanent remission if the drugs are stopped.[25] The others will experience recurrent thyrotoxicosis. Thus, most patients will require another form of treatment if this therapy fails.

Radioactive Iodine Therapy

Treatment of the thyroid with ^{131}iodine is very effective in Graves' disease. It is usually given in doses of about 3 to 10 millicuries of ^{131}I. It is attractive therapy since no operation is necessary, it is less expensive than thyroidectomy, and it can be given to patients who are considered to be poor operative risks. In some clinics it has become the treatment of choice and has even been given to children.[14] We disagree with this philosophy and usually limit its use to individuals 35 to 40 years of age or older who no longer want to have children. Radioiodine should not be given to pregnant women since ^{131}I crosses the placenta and could ablate the fetal thyroid. It is also rarely given if the uptake of iodine by the thyroid is very low since, in these instances, a very large dose of radiation would be necessary. Another disadvantage is that an increasing incidence of hypothyroidism of about 3 per cent per year occurs after standard radioiodine therapy presumably for as long as a patient lives.[5, 13] Thus, insidious hypothyroidism may occur many years after treatment in an individual who is unaware of this problem. Ten years after radioiodine therapy, for example, about 40 per cent of recipients have developed hypothyroidism. New regimens using lower doses of radioactive iodine are being tried in an attempt to combat this progressive dysfunction.[21] However, they appear to suffer from the fact that an increased number of patients require two or more treatments to produce a euthyroid state. Thus, therapy is prolonged. Furthermore, while hypothyroidism is reduced initially,[6] it is not known if this therapy will also result in progressive hypothyroidism since long-term follow-up studies are unavailable. Three other potential complications of ^{131}I therapy should also be considered:

Leukemia

An increased incidence of radiation-induced leukemia has been observed in survivors of the atomic bomb explosion of Hiroshima who were exposed to 20 to 40 rads of radiation.[16] An increased risk of leukemia and of solid tumors has also been reported in children who were exposed in utero to diagnostic x-ray films in a dose range of only 0.5 to 2.0 rads.[23] Because of this potential risk, a national survey was performed to evaluate the risk of leukemia following radioactive iodine treatment for Graves' disease.[22] After a mean follow-up period of 6.5 years, patients with Graves' disease treated by radioactive iodine demonstrated no increase in leukemia when compared with a surgically treated group. The mean whole-body dose of radiation exposure in this group of patients was approximately 11 rads, the blood dose was about 15 rads, and the bone-marrow dose range was 7 to 13 rads. As utilized today, most radioiodine treatment regimens result in lesser amounts of exposure to the patient.

Genetic Abnormalities

Another potential hazard of radiation therapy which is difficult to assess is the possibility that damage could occur to the gonads, thus producing genetic abnormalities in future generations. Such difficulties have not been recognized thus far in patients treated with radioiodine.[4] However, not enough patients have been studied to produce reliable statistics. It is largely for this reason that radiation therapy should be given only after considerable forethought to patients who later want to have children.

Carcinoma of the Thyroid

Risks After External Irradiation. It is well known that low-dose external irradiation to the thyroid area is associated with an increased incidence of benign and malignant tumors of the thyroid and of the salivary glands.[7] Irradiation has been linked to the formation of parathyroid adenomas as well. Radiation therapy was given in this country for three major reasons: to shrink the thymus; to shrink the tonsils and adenoids and thus prevent the need for tonsillectomy; and to treat severe acne in adolescents and young adults.

Sudden crib death in infants was thought to be caused by pressure from an enlarged thymus upon the trachea. A small amount of radiation therapy, about 50 to 450 rads, was found to be quite effective in reducing the thymus in infants. Children about 6 years of age received a mean dose of about 800 rads to the throat area to shrink tonsils and adenoids. X-ray therapy appeared to be efficacious in treating acne; patients received up to 1500 rads to the face.

Other individuals also received treatment for hemangiomas, cervical lymphadenitis, and many other miscellaneous conditions. Unfortunately, the thyroid area was rarely shielded when treatments were given. Now, 20 to 30 years later, a higher incidence of benign and malignant tumors of the thyroid is being discovered. Several studies suggest that a radiation dose as low as 6.5 rads to the thyroid bed may be associated with an increased incidence of malignant tumors of the thyroid and that the in-

cidence of thyroid cancer increases in a linear fashion up to about 1500 rads.[18] There is not a great deal of information concerning radiation-induced carcinogenesis above this dose; however, many investigators feel that the risk is less at higher doses since more thyroid cells are destroyed.

We and others have found that about 25 per cent of individuals who received neck irradiation of 1500 rads or less have a palpable abnormality of the thyroid gland.[12, 20] Two to nine per cent of all irradiated individuals have been found to have a carcinoma of the thyroid gland and about 9 per cent have developed a benign nodule. Fortunately, most of the malignant thyroid lesions are papillary or follicular carcinomas and the prognosis in these young adults is good if they are treated appropriately.

RISK AFTER RADIOACTIVE IODINE TREATMENT FOR GRAVES' DISEASE. Administration of radioactive iodine is known to produce an increased incidence of thyroid cancer in rats, especially if given together with PTU.[10] For this reason, the hazard of ^{131}I therapy for Graves' disease was evaluated. In 1974, the Cooperative Thyrotoxicosis Therapy Follow-up Study was published.[8] It concluded that there was no evidence that radioiodine therapy is associated with an increased incidence of cancer of the thyroid. This result may be due to the fact that radioiodine therapy, as given at that time, generally resulted in an exposure of 5000 to 10,000 rads to the thyroid gland, a dose much larger than that given to externally radiated patients who developed cancer. Presumably, this larger dose kills many cells rather than changing them in some way that later produces neoplasia. These results, however, should not be accepted as conclusive since the mean follow-up of these patients was only eight years. Dr. Brown Dobyns, chairman of this study, has recently written that follow-up data of 20 to 30 years are necessary before definitive conclusions can be reached.[8] Another unresolved question relates to whether or not the new low-dose radioiodine treatment regimens now being tried are more dangerous from a carcinogenic point of view, since more cells would be expected to remain viable, perhaps in a modified form.

SURGICAL TREATMENT

Because of the potential long-term risks of radioiodine therapy, the popularity of thyroidectomy as definitive treatment for Graves' disease is once more growing in some centers. We currently operate on many individuals who are 35 years of age or younger. Older patients who have a nodule of the thyroid, or who do not want radioiodine therapy, are also operated upon. Subtotal thyroidectomy is also the treatment of choice for Graves' disease during the first two trimesters of pregnancy, and for some children.

The major advantage of operation is the rapid reversal of the thyrotoxic state, which permits the patient to be quickly rehabilitated. It also appears that hypothyroidism is both initially and progressively lower with this therapy than with radioactive iodine treatment as it is usually given. The disadvantages include the stress of an operation, the risk of a

general anesthetic, a greater expense than the other forms of therapy, possible cosmetic difficulties, and finally, the risk of potential complications of operation, especially vocal cord paralysis and hypoparathyroidism. Fortunately, the incidence of each of these complications is low in most series.

Preparation for Operation

In 1923, Plummer first demonstrated that iodine blocked the release of thyroid hormone in patients with Graves' disease.[19] This finding was a major achievement. Now, for the first time, the patient with thyrotoxicosis could be partially or completely controlled prior to operation. Iodine treatment resulted in a marked decrease in morbidity and mortality, both of which were very high prior to that time. The next advance in therapy occurred in 1943, when Astwood introduced the thiocarbamide drugs, such as propylthiouracil.[2] These agents act by blocking the organification of iodine within the thyroid gland and appear to diminish the peripheral conversion of T_4 to T_3 as well. When these drugs are used with iodine, patients can be operated upon with an even lower morbidity, for now, virtually all patients can be brought to a euthyroid state. Finally, the recent introduction of propranolol, a beta adrenergic receptor blocker, has made the operation for Graves' disease still less risky.[26] Now cardiac arrhythmias and tachycardia can be more easily treated.

In Table 1, some of the more common regimens used to prepare patients with Graves' disease for operation are listed. Our standard protocol consists of treatment with propylthiouracil (PTU), 150 to 600 mg orally per day, or methimazole (Tapazole), 15 to 60 mg by mouth daily in three or four divided doses until a euthyroid state is obtained. Usually this takes at least four to six weeks. Then, oral iodine as saturated solution of potassium iodide (SSKI) or Lugol's solution is added to the PTU or Tapazole regimen for about 10 days before operation in a dose of five drops twice a day. For faster control, iodide can be added soon after the PTU is started and before the patient has become euthyroid. The iodine serves to make the thyroid gland firmer and decreases its vascularity, thus diminishing the loss of blood at operation. If a patient becomes hypothyroid on this regimen, thyroid hormone can be added to the other medications. Some surgeons routinely use thyroid hormone with PTU since they feel that this combination makes the gland smaller and easier to operate upon.

Table 1. *Preoperative Treatment Regimens for Graves' Disease**

Iodine alone
PTU + iodine
PTU + thyroxine + iodine
PTU + propranolol + iodine
Propranolol + iodine
Propranolol alone

*Most of our patients are prepared for operation by the use of propylthiouracil (PTU) and iodine, with or without propranolol.

If a patient has severe symptoms of tremor, nervousness, or tachycardia, oral propranolol, 10 to 40 mg four times daily, can be added to the PTU regimen and will generally rapidly relieve these symptoms. Once started, we continue oral propranolol up to the time of operation. None of our patients has experienced complications of myocardial depression during anesthesia at this dosage level. However, the drug should not be given to patients with poor myocardial function or with asthma. Postoperatively, all PTU and iodine are stopped; if propranolol has been given until operation it should be continued postoperatively, tapered, and then stopped.

We do not favor the use of propranolol alone or only with iodine for the routine preoperative preparation of all of our patients.[3, 17] While this therapy clearly decreases the time of preoperative preparation to one to two weeks in many patients, we feel that it may not offer the same degree of safety as does the PTU and iodine regimen. Several cases of thyroid storm, fever, and tachycardia have been reported in patients who were taking propranolol in this dosage range.[11] We have used propranolol therapy alone without any difficulty for preparation of a small group of patients who were allergic to PTU or iodine. In such patients it is essential that they continue to take propranolol for several weeks after operation, since they are still grossly thyrotoxic immediately after operation, although the peripheral manifestations of their disease have been blocked.

Operative Technique

Our standard operation for treatment of the diffuse goiter associated with Graves' disease is a subtotal thyroidectomy. By this it is meant that most of the thyroid gland is removed and only a small remnant of the posterior capsule of each thyroid lobe is left in place. If it is recognized that the patient with Graves' disease has a definite nodule, a lobectomy should be performed on that side. If carcinoma is found on frozen section, our policy is to perform a total or near-total thyroidectomy, as was done in one of our patients.

No more than 8 to 10 gm of total thyroid tissue should be left in the neck at the end of this procedure regardless of the size of the goiter, or hyperthyroidism may recur. In general, we tend to leave less, usually only several grams of tissue on each side, especially in young patients, who are known to have a greater incidence of recurrent disease after operation.[15]

As in all thyroid operations, the best results are obtained by experienced neck surgeons. One must have a firm understanding of the anatomy of this region, of the physiology of Graves' disease and, finally, of the potential complications that may occur during and after operation. For best results, one must operate in a meticulous, careful, unhurried manner. The general principle of maintaining a bloodless field is very important; however, it is sometimes difficult to achieve since these glands generally bleed more profusely than usual even when they have been carefully prepared.

The two most important hazards of operation which must be carefully avoided are an injury to the recurrent laryngeal nerves and extensive damage to the parathyroid glands resulting in permanent

hypoparathyroidism. The surgeon should identify the recurrent laryngeal nerve on both sides and be cognizant that it is in greatest danger of injury in the area near its entry into the larynx. Here it is immediately adjacent to thyroid tissue. If bleeding occurs in this area, never clamp or coagulate blindly. Furthermore, one should never ligate the inferior thyroid artery laterally as a single vessel. This is attractive since it diminishes the vascularity of the gland. However, the combination of ligation of the inferior and superior thyroid arteries and mobilization and removal of most of each thyroid lobe may be sufficient to devascularize the parathyroid glands. Thus, most cases of permanent hypoparathyroidism are probably not caused by removal of all parathyroid tissue but rather result from ischemia and necrosis of these glands. The correct operative approach to prevent this complication is the careful ligation of the small vessels immediately adjacent to the thyroid lobe, distal to the area in which they supply the parathyroid glands. When these techniques are utilized, surgical therapy for Graves' disease can be safe and rewarding.

Clinical Series

Between July, 1972, and July, 1977, 75 patients on an adult surgical service of the University of Chicago Hospitals received thyroidectomy as their first definitive therapy (Table 2). Sixty-eight (91 per cent) of these individuals have been followed for one year or longer; their mean follow-up time is 36 months. Seven other patients (9 per cent) were lost to follow-up before one year and thus data concerning their postoperative thyroid functional status are not included in this report. Sixty-four patients were women and eleven were men. Their ages ranged from 13 to 60 years; however, the mean age was about 26 years.

Prior to any treatment the thyroid function tests of this group of patients were elevated. Mean serum total thyroxine (TT_4) was 19.9 ± 8.2 μg per ml (mean ± S.D.) (normal: 4.2 to 8.7 μg per 100 ml) and free thyroxine index (FTI) was 29.1 ± 12.3 (normal: 4.5 to 8.5). As described above, the hyperthyroid state was treated in most instances with either PTU or methimazole with iodine. Propranolol was utilized with other drugs, or was used alone when patients were intolerant of other medications. Immediately preoperatively, thyroid function tests usually were normal: TT_4 was 7.5 ± 3.3 μg per 100 ml and FTI was 8.2 ± 3.4. Subtotal thyroidectomy alone was performed in 74 individuals. Total thyroidectomy was performed in one patient who was found to have a papillary carcinoma as well.

No patient required a blood transfusion and no deaths occurred. Postoperatively, no significant wound hematomas or wound infections occurred. One patient had a transient recurrent nerve injury. Two others manifested prolonged hypocalcemia, although one returned to normal values spontaneously. The other patient has normal circulating parathyroid hormone values but is hypocalcemic and requires vitamin D therapy intermittently. The mean postoperative hospital stay of all patients was 4.4 ± 1.2 days.

Eighty-two per cent of patients remained euthyroid during this

Table 2. *Results of Subtotal Thyroidectomy as Primary Therapy for Graves' Disease*

	NUMBER OF PATIENTS	PER CENT
Operation		
Subtotal thyroidectomy	74	
Total thyroidectomy	1	
TOTAL	75*	
Complications of operation		
Mortality	0	
Wound infection	0	
Hemorrhage	0	
Transient recurrent laryngeal nerve injury	1	
Hypoparathyroidism		
Permanent	1	
Transient	1	
Postoperative thyroid function in 68 patients followed one year or longer (mean follow-up time 36 months)		
Euthyroid	56	82
Hyperthyroid chemical as well as symptomatic	8	12
Hypothyroid	4	6
TOTAL	68	

*Age range: 13 to 60 years. Mean age: 25.9 ± 6.8 years.

follow-up period. The incidence of recurrent hyperthyroidism, defined as either a recurrence of symptoms or FTI determinations greater than 8.5, is 12 per cent. Several individuals who feel well but have mildly elevated thyroid function tests are included in this group. Postoperative hypothyroidism, defined as serum TT_4 and FTI values below 4.2 μg per 100 ml and 4.5, respectively, occurred in only 6 per cent of patients, including the individual who had a total thyroidectomy. We have been pleased with these functional results and with the low morbidity in these patients.

SUMMARY

Hyperthyroidism of Graves' disease may be treated very effectively by antithyroid pills, such as PTU and Tapazole, by radioactive iodine therapy, and by subtotal thyroidectomy. Each form of therapy has advantages and disadvantages, and thus treatment should be individualized.

While therapy with radioactive iodine would appear to be ideal since it does not require an operation and is less expensive than surgical management, it suffers from a high rate of progressive hypothyroidism and from the fact that the time until a euthyroid state is obtained is often prolonged.

In addition, the long-term carcinogenic risk of the therapy for thyroid neoplasia has never been completely defined since the data most often quoted have a mean follow-up time of only eight years. Furthermore, new "low-dose" radioiodine regimens may be more dangerous in this regard.

Subtotal thyroidectomy, while not totally without complications, remains a rapid, safe, and effective treatment for Graves' disease. The careful use of propranolol has facilitated the preparation of some patients and has lessened the risk of operation. Thyroidectomy should remain the treatment of choice for young adults with this disease.

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The Approach to the Irradiated Thyroid

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The patient with a history of head and neck irradiation poses a clinical problem that is controversial both diagnostically and therapeutically. This article proposes to elucidate the problem of the irradiated thyroid in terms of demography, pathology, diagnosis, and treatment, to present our experience with the problem, and to propose a rational approach to the irradiated thryoid patient.

Historical Perspective

The roots of this problem lie in Friedlander's work of 1907[27] in which he suggested the use of external irradiation for the treatment of infant thymic enlargement. The therapeutic applications of external irradiation were broadened by Witherbee's proposal in 1924[68] of its value in treating childhood tonsillitis and pharyngitis. For the next several decades, irradiation as treatment for various dermatologic, inflammatory, and infectious conditions of the head, neck, and chest gained wide acceptance.

The potential hazards of such therapy remained unrecognized until 1950, when Duffy and Fitzgerald[20] reported that 9 of 28 children with thyroid carcinoma had sustained prior head and neck irradiation. Subsequent evidence for the carcinogenic role of this therapy in thyroid and other head and neck neoplasia was provided by others as well.[56, 57]

The first prospective effort to locate and screen patients with a history of prior thymic irradiation for thyroid abnormalities was described in 1967 by Pincus.[46] By 1973, when DeGroot and Paloyan[14] documented prior irradiation in 40 per cent of adults with thyroid cancer, it had become clear that the risk of developing thyroid cancer was significantly enhanced by prior irradiation, and that the risk persisted well into adult life.

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Since then, enhanced patient and physician awareness and subsequent projects of patient recall and screening have generated data that describe the problem of the irradiated thyroid and provide rationales for the varying diagnostic and therapeutic measures employed today.

SOURCE AND SCOPE OF THE PROBLEM

Etiology

The association of thyroid carcinogenesis and irradiation suggested by clinical studies is supported by animal experiments.[62] Although the precise nature of this effect remains speculative, the postulated mechanism involves injury to the thyroid, both from the direct effect of the external irradiation itself and from the indirect effect of diffusible free radicals generated from irradiated cell water. The macromolecular genetic contents of the nucleus are especially vulnerable to such ionizing effects and presumably undergo genetic alterations that result in cellular dedifferentiation and neoplastic growth patterns.

A second major factor in the tumorigenic effect of irradiation on the thyroid relates to the role of thyroid stimulating hormone (TSH) in thyroid proliferative disorders. Studies by Doniach[17, 18] have shown TSH to function in a permissive role in thyroid neoplasia. In one study,[18] irradiated rats with TSH suppression developed fewer benign and malignant thyroid tumors than did those with normal or elevated TSH levels. Presumably, the loss of functioning thyroid tissue by direct irradiation damage feeds back on the hypothalamic-pituitary axis to maintain elevated TSH levels. Accordingly, Astwood[3] showed in humans that some thyroid nodules decreased in size or disappeared after TSH suppression by exogenous thyroid hormone. Such data provide the rationale for thyroid suppressive therapy in irradiated patients.

The dose range of head and neck irradiation associated with thyroid neoplasia has been widely studied in animals and man. One review[19] indicates that the optimal carcinogenic dose in rats and man is 500 to 2000 rads, which is equivalent to the calculated dose to the thyroid received by infants irradiated for thymic hypertrophy.[24] While doses as low as 6.5 rads have been implicated in thyroid carcinogenesis,[39] Hemplemann[33] and Dolphin[16] have shown a linear increase in the risk of thyroid cancer over the calculated thyroid dose range of 20 to 1125 rads. Between 2000 and 3000 rads, however, there is a gradual decrease in risk of carcinogenesis with a marked decrease in risk beyond 3000 rads.[37] This decreased risk after higher doses is presumed to be the result of the total or near-total loss of viable thyroid tissue from higher-dose irradiation damage.

The specific indications for irradiation include a variety of inflammatory, infectious, hypertrophic, and neoplastic processes of the head, neck, and upper thorax. Up to 80 per cent of patients were irradiated for hypertrophied tonsils or adenoids in one series[23] and up to 30 per cent for thymic hypertrophy in another.[48] Other conditions such as cervical adenopathy, acne, sinusitis, and tinea capitis were irradiated less frequently.

Prevalence and Demographic Variables

Though the biological significance of irradiation-associated thyroid cancer has been questioned by some, there can be no doubt that nodular thyroid disease and cancer associated with a history of prior irradiation represent a significant portion of thyroid pathology.

The prevalence of irradiation-induced thyroid disease is better appreciated in light of the prevalence of nodular thyroid disease in general. In a nonirradiated population, the prevalence of nodular goiter approaches 3 per cent,[63] whereas the prevalence of unselected thyroid cancer in the United States is .0036 per cent or 36 cases per 1,000,000 population.[13] It was estimated that in 1976, there would be 8100 new cases of thyroid cancer diagnosed and 1150 deaths from thyroid cancer.[69]

In contrast to these figures, a population of 2189 irradiated patients demonstrated a prevalence of nodular disease of 32.6 per cent.[53] Of these, over one-third were proved to have cancer, for a prevalence of irradiation-induced thyroid cancer of 11.7 per cent in the population at risk. A second population of 100 irradiated patients revealed similar results: a 26 per cent prevalence of nodular disease and a 7 per cent prevalence of thyroid cancer.[48] Several prospective screening programs have shown prevalences of irradiation-induced nodular thyroid disease ranging from 15.7 to 35.7 per cent,[9, 10, 15, 32, 36, 41] while several retrospective surgical-pathological analyses[30, 44, 58, 60] have shown that of those patients operated for post-irradiation thyroid nodularity, from 23 to 54 per cent are proved to have thyroid cancer.

The significance of the above figures has been questioned by the findings of a 50 per cent prevalence of thyroid nodules in unselected autopsies,[40] and 13 to 28.4 per cent prevalence rates of thyroid carcinoma in unselected autopsies in the United States and Japan, respectively.[52] These data suggest that irradiation does not necessarily increase the incidence of thyroid nodularity or cancer. However, Favus et al.[22] consider such a conclusion unwarranted inasmuch as such studies tend to select an older population in which a natural increase in the incidence of thyroid cancer is known to occur. In fact, Oertel and Klinck[42] found only one thyroid cancer among 137 autopsies performed on United States military personnel between the ages of 20 and 39, an age group more closely corresponding to that which is at risk for post-irradiation thyroid disease.

The problem of post-irradiation thyroid neoplasia can be further defined in terms of demographic characteristics of sex, age at initial therapy, and latency (time between initial therapy and diagnosis of disease). These characteristics have been most closely studied in the large prospective screening programs of the last several years. The Michael Reese survey of 5266 patients[53] indicates the population at risk to be 58.4 per cent female, with a mean age at initial therapy of 5.1 years and a mean latency of 20.2 years. This correlates well with the data of other programs,[10] while some reports describe latency periods as long as 40 years.[30]

Considerable attention has been paid to determining if such demographic characteristics might serve as indicators of the risk of malignancy among the irradiated population. Hemplemann et al.[34] found, among

3000 individuals irradiated in infancy for thymic enlargement, the risk of developing thyroid cancer to be increased 2.3-fold in females versus males, 3.4-fold in Jews versus non-Jews, and linearly increased in proportion to irradiation dose, though they found no significant relationship to age. Analysis of the Michael Reese data[23, 29] using linear regression techniques also revealed that nodular thyroid disease was linearly correlated with radiation dose but not with age at the time of treatment or latency. Nodular thyroid disease was more frequently detected in females, but the chance that a given nodule was cancerous was independent of sex. Furthermore, they determined that no distinction between benignity and malignancy could be made on the basis of any of the variables measured. It remains, therefore, that with the exception of the calculated dose of thyroid radiation received, demographic variables are generally not helpful in defining the population at risk for thyroid cancer following irradiation.

PATHOLOGY OF THE IRRADIATED THYROID

Histopathologic Characteristics

Data generated by numerous surgical-pathological analyses of recent years have revealed a number of characteristics that define and distinguish in a general way the pathology of the irradiated thyroid.

Of greatest significance is the frequent occurrence of cancer in the irradiated glands. These malignancies tend to be well differentiated, with papillary, follicular, and mixed papillary-follicular types predominating. Most of the larger series report up to a 90 per cent incidence of papillary or mixed papillary-follicular cancers with markedly fewer pure follicular cancers, in the range of 5 to 15 per cent.[23, 32, 60] Of note are several series that report occasional occurrences of medullary or anaplastic carcinoma in the post-irradiated thyroid.[5, 10, 36, 58] The cancers tend to be small, with approximately 50 per cent of the malignant nodules equal to or less than 1 cm in size and very few greater than 3 cm in size.[10, 53, 60] Furthermore, they demonstrate significant multicentricity and bilaterality in up to 30 to 50 per cent of cases.[10, 23, 60] This contrasts with data on nonirradiated thyroid pathology in which multinodularity speaks for benignity.[28] Although these tumors are only rarely associated with distant metastases,[35, 44] they are characterized by a significant incidence of regional lymph node involvement approaching 50 per cent in several studies[5, 36, 44] and capsular or vascular invasion in up to 30 per cent of cases.[23, 60]

Concomitant with the increased numbers of thyroid cancers in these patients is a marked increase in the incidence of benign thyroid disease. Straus and Spitalnik[59] describe a wide variety and high incidence of benign pathology among excised post-irradiated thyroids, including focal hyperplasia (88 per cent), thyroiditis (67 per cent), adenomas (51 per cent), colloid nodules (51 per cent), Hurthle cell changes (42 per cent), and fibrosis (25 per cent).

From the above data, it is obvious that benign and malignant pathology often coexist in the same gland, with Favus et al.[23] reporting up to 76

per cent incidence of benign pathology in their patients with proven thyroid cancer. Frequently, the cancerous lesion is located in an area of the gland distinct from the clinically detectable nodule for which the operation was performed, which has been reported in as many as 67 per cent of cases in one series.[36]

Natural History of Post-Irradiation Thyroid Cancer

There is little direct prospective data on the natural history of post-irradiation thyroid cancer. What is known has been inferred from retrospective analyses which suggest that it behaves in a biologically similar manner to its nonirradiated counterpart.

Autopsy studies and follow-up studies of patients treated with less than total thyroidectomy for papillary carcinoma indicate the lesion to be innocuous and suggest that microscopic foci of papillary cancer are not likely to develop into "clinical" cancers.[21, 52] Such data have been the foundation of a philosophy of therapeutic conservatism proposed by Sampson[50] and Crile.[12] Furthermore, Franssila[25] has shown that the prognosis in papillary thyroid cancer relates primarily to the extent of the primary tumor and age of the patient, suggesting multifocal unpalpable disease to be of little clinical significance.

Numerous reports in the literature, however, support the view that irradiation-associated thyroid cancer is not necessarily a "benign" condition. First, several reports[5, 10, 36, 58] have documented the occurrence of medullary and anaplastic cancers in irradiated thyroids. Additionally, Wilson et al.[67] reported a 10 per cent incidence of distant metastatic disease and a 3.4 per cent death rate from thyroid cancer in their series of post-irradiation patients followed more than 10 years. Other reports in the literature support the occurrence of distant disease and cancer-related death in the irradiated population.[5, 35, 44, 53]

The problem of recurrence of irradiation-related thyroid cancer is also significant and well documented. Schneider et al.[53] showed that of 50 patients undergoing less than total thyroidectomy, 36 per cent later developed clinically detectable discrete thyroid nodules, and of 25 patients undergoing more than one operation, 33 per cent were found to have carcinoma on subsequent exploration. Similarly, Block[5] reported a 22 per cent incidence of recurrent thyroid cancer requiring reoperation in patients initially undergoing less than total thyroidectomy. These data are particularly significant when compared with those of Tollefsen et al.[61] who found only a 4.6 per cent clinical recurrence rate among nonirradiated patients undergoing less than total thyroidectomy for papillary carcinoma.

DIAGNOSTIC APPROACH

The most important factor in detecting irradiation-associated thyroid disease is patient and physician awareness of the problem. The mass screening and patient recall programs have been responsible for a large number of patients at risk receiving appropriate attention, with a

significant remainder coming to their private doctor as a result of lay education by media coverage.

Documenting a history of irradiation may involve more than the patients' memory of such treatments, as Albert and Onran have shown a 23 per cent incidence of false negative histories for irradiation when only the patient was questioned.[1] This is based in part on the fact that many patients were irradiated in infancy and thus were unaware of their therapy.

Given a history of irradiation, the clinical examination of the patient remains the first, and for some the only, diagnostic measure required, with particular attention paid to nodularity or diffuse enlargement of the gland and the presence of palpable cervical nodes.

The thyroid scan is likewise an important diagnostic measure. Burke[7] enumerates several isotopic agents that have been used clinically and experimentally, including ^{131}I, ^{123}I, ^{99m}Tc, ^{67}Ga, ^{131}Cs, ^{75}selenomethionine, the latter three being in limited use due to their high incidence of false negative results. While ^{131}I is still in wide use because of its availability and its ability to differentiate functioning from nonfunctioning nodules by uptake characteristics, Pinsky and Ryo[47] have concluded that because of decreased cost, radiation dose, and imaging time, the preferred isotopic agent is ^{99m}Tc-pertechnetate when used with a gamma (scintillation) camera and pinhole collimator. Fluorescent thyroid imaging is another useful scanning technique though it is still under preliminary investigation.[45]

Sonography, while useful in differentiating cystic versus solid lesions, and thus influencing one's suspicion of benignity versus malignancy, is generally limited in sensitivity to lesions between 1 and 4 cm in diameter.[6]

Numerous biochemical tests are available to help assess the irradiated thyroid patient. Assays for T_3, T_4, TSH and antithyroid antibodies are reliable and useful in determining a patient's thyroid function or predisposition to autoimmune thyroiditis, but such tests have been found to be of no help in distinguishing benign versus malignant thyroid disease.[10, 41, 54]

In contrast, the serum thyroglobulin level (HTg) has been shown to be a relatively reliable "marker" for thyroid malignancies. Van Herle[64] has shown that the mean preoperative HTg level is elevated up to five times normal in patients later proved to have thyroid cancer, and that these levels fall to normal range after surgery. High levels in patients with documented metastases have suggested a role for this assay as a means of following patients with known differentiated thyroid cancer.

The most reliable diagnostic test is the obtaining of tissue. Short of open biopsy, the use of needle biopsy and needle aspiration has received some attention in this regard. Vickery[65] reviewed 1129 thyroid needle biopsies and found no serious complications, adequate tissue obtained in 90 per cent of cases, and a 93 per cent correlation of biopsy and operative diagnoses. In those patients with cancer, there were no proven instances of carcinomatous seeding of the needle tract. The applicability of this

technique to irradiated patients is questioned, however, because of the increased suspicion of cancer, increased incidence of multifocality, and decreased size of lesions in that population.

Chu et al.[11] reviewed 50 cases involving fine needle aspiration of the thyroid and found no cases of false negative and only one case of false positive cytology among those who later underwent surgery. However, for the same reasons as apply to needle biopsy, this diagnostic technique has not found wide use in evaluating the irradiated thyroid patient.

Aside from the clinical examination, only the thyroid scan among the tests enumerated above has gained wide acceptance in the evaluation of the irradiated thyroid patient; and, despite its accepted role in patients with equivocal physical findings, significant controversy exists over its routine use in assessing patients with a history of irradiation.

Arguments against routine scanning focus on the relative reliability and sensitivity of careful physical examination, avoidance of further radiation exposure, and elimination of the additional cost. In one series, Hamburger and Stoffer[32] found that of 211 patients who underwent ^{99m}Tc scans, only one had a scan positive for a lesion missed on physical examination (false negative physical findings of .5 per cent), whereas 15 negative scans were obtained in patients with palpable nodules (false negative scan findings of 7.1 per cent). Confirmation of increased sensitivity of physical versus nuclide examination of the thyroid is provided by others as well.[10, 60]

Conversely, arguments favoring routine scanning point to data indicating increased sensitivity of scanning techniques over physical examination and to the fact that with ^{99m}Tc, the radiation dose to the thyroid is negligible (approximately 1 rad). The Michael Reese data[23] strongly support the use of routine thyroid imaging. In that study of 1056 irradiated patients, abnormal scans were obtained in 26 per cent of patients, whereas abnormal physical findings were present in only 16 per cent of patients. Further, there were only 10 instances of a normal scan associated with abnormal physical findings (false negative scan rate of .3 per cent), whereas 114 patients normal on physical examination had one or more discrete abnormalities on scan (false negative physical examination rate of 12.9 per cent). Of those classified as having nodular disease, 97 per cent were identified by scan alone versus 49 per cent by physical examination. Additional support for routine thyroid imaging lies in the ability of the ^{99m}Tc scans to detect lesions as small as 5 mm,[2] which is considerably smaller than those that can be detected by palpation.

THERAPEUTIC APPROACH

Interest in establishing guidelines for the therapeutic approach to the irradiated thyroid led to the formation of a workshop on "the late effects of irradiation to the head and neck in infancy and childhood" conducted by the National Cancer Institute. The recommendations of the participants specify treatment based on one of three diagnostic categories of physical

findings.[4] Category I patients (normal on palpation) are followed by careful yearly examination. If a scan in these patients reveals a "cold" area, the recommendation is for suppressive doses of thyroid hormone and frequent follow-up examinations, with surgery recommended if the lesion becomes palpable. Category II patients (discrete nodules on palpation) are generally recommended to have surgery, unless the nodules are small, poorly demarcated, and the scan normal, in which case thyroid suppression and frequent re-examination is suggested. Category III patients (diffuse enlargement without nodules) are recommended to have thyroid suppressive therapy regardless of scan findings, with surgery indicated only if a nodule becomes palpable.

Few would argue with the recommendation of frequent reexamination of irradiated patients for whom surgery is not indicated, and most authorities concur with the use of thyroid suppressive therapy, either routinely or in cases of equivocal findings or diffuse thyroid enlargement without nodules. Robbins[49] recommends its routine use based on the animal experiments and human data which support the concept of the permissive role of TSH in thyroid neoplasia. Similarly, Shimaoka[55] found a 49 to 73 per cent response rate to TSH suppression in 114 patients with nontoxic goiters, noting specifically that response (i.e., shrinkage of nodules) occurred in a comparable percentage of irradiated versus nonirradiated patients. Further support for thyroid suppression lies in the increased palpability of discrete nodules in patients treated with TSH suppression for initially equivocal findings or diffuse enlargement. Finally, Schneider et al.[53] have shown that thyroid suppression significantly reduces the incidence of recurrent nodular disease in irradiated patients having undergone prior thyroid surgery.

While most workers agree with the nonoperative management described above, significant controversy exists over the specific indications for surgery and the extent of resection when surgery is indicated.

As proposed by the National Cancer Institute's Workshop,[4] there are those who favor surgery only for discrete palpable nodules of significant size. Fratkin and Sharpe,[26] relying more on thyroid imaging which they use routinely, differ in this approach to the Category I patient by recommending surgery if the scan reveals a discrete "cold" area, even if palpation is normal. Conversely, when examination reveals nodular disease not detected by scan, they recommend thyroid suppression, reserving operation for patients in whom the nodule does not regress within six to 12 months. This approach of thyroid hormone therapy and observation in selected patients with nodular thyroids has been adopted by others as well.[8, 38]

A more conservative approach has been proposed by Crile.[12] Preferring to utilize lifelong thyroid suppression in patients with prior irradiation, he recommends aspiration biopsy if nodules develop, and only if unusual or abnormal cellularity is detected does he recommend resection.

The majority of the current authorities, however, favor surgery whenever examination or scan reveals discrete nodular disease,[23, 35, 44] relying strongly on the ability of the scan to detect significant disease in the absence of palpability. Kaplan[35] goes further in recommending

surgery on glands of abnormal consistency, firmness, or enlargement without discrete nodules, if such findings remain after six months of thyroid suppression and antithyroid antibodies are negative.

When surgery is indicated, several workers recommend a conservative approach of partial thyroidectomy. As stated above, Crile[12] suggests reserving operation for those in whom thyroid suppression fails and from whom positive aspiration biopsy is obtained. Given such circumstances, he recommends excision of the affected lobe and isthmus and a subtotal contralateral lobectomy, believing that for clinically apparent unilobar disease, total thyroidectomy subjects the patient to an unwarranted risk of tetany. Similarly, the NCI's Workshop[4] recommends that resection be only as extensive as is required to remove all clinically abnormal tissue. Sampson[50, 51] recommends local removal of only the larger nodules detected, based on the higher morbidity of total thyroidectomy for a "harmless condition that is cancer in name alone." Block[5] feels that the initial procedure should entail excision of the involved lobe with partial contralateral lobectomy. If frozen section confirms carcinoma, then completion of a total or near-total thyroidectomy is recommended. In cases in which positive permanent sections contradict originally negative frozen sections, reoperation for total thyroidectomy is recommended if multicentricity or bilateral lobe involvement is confirmed.

In contrast to this limited resection approach is the view shared by many:[31, 43, 48, 60] that the initial surgical approach to the irradiated thyroid patient should be total or near-total thyroidectomy even in the absence of a tissue diagnosis at the time of operation. The rationale for such an approach is based on the natural history and pathologic characteristics of the disease. Reviewed by Kaplan[35] and Paloyan,[43] these characteristics include: the high incidence of carcinoma in the irradiated population; the high incidence of multicentricity and bilaterality of clinical disease; the high incidence of occult disease present in the lobe contralateral to the one with clinical pathology; the high incidence of recurrence when less than total thyroidectomy is performed, with the concomitant increase in morbidity when reoperation is required; the occasional unreliability of frozen section diagnosis; and the facilitation of postoperative radio-iodine scanning and treatment for metastatic disease when all normal thyroid tissue has been removed.

Of those supporting this approach, most recommend dealing with the cervical nodes by biopsying clinically suspicious nodes, and if positive, proceeding with a modified neck dissection with preservation of the sternocleidomastoid muscle and spinal accessory nerve if possible.[43, 48] Swelstad et al.[60] recommend paratracheal node dissection only.

Those critical of this more aggressive approach have cited the greater likelihood of recurrent nerve or parathyroid damage with total or near-total versus subtotal thyroidectomy or lobectomy. Many of the current reports, however, indicate minimal morbidity from the total or near-total thyroidectomy approach. In Kaplan's series of 54 patients so treated,[35] there were no cases of permanent recurrent nerve injury, permanent hypoparathyroidism, or hematoma, and only one wound infection. In Paloyan's series of 70 patients,[43] there was a 2.8 per cent incidence of

permanent hypoparathyroidism and a 1.4 per cent incidence of permanent recurrent nerve palsy, whereas Swelstad et al.[60] reported only one permanent nerve injury and one case of permanent hypoparathyroidism in 68 cases of total or near-total thyroidectomy. There was no operative mortality reported in any of the series reviewed.

CLINICAL EXPERIENCE

Materials and Methods

Our experience with surgery for the irradiated thyroid includes 112 patients treated from 1964 through 1977. The indications for surgery included palpable thyroid abnormalities (including diffuse goiter, discrete nodularity, or ominous cervical adenopathy) or abnormal thyroid scans.

Diagnostic studies in these patients have been limited to physical examination and thyroid scan. Initially the scanning technique employed ^{131}I, but more recently we have used technetium ($^{99m}TcO_4$) via scintillation camera with a pinhole collimator. Neither echography nor percutaneous needle aspiration was employed in this series because we feel that surgical exploration is warranted in patients with a history of head and neck irradiation who present with physical or scan evidence of thyroid abnormalities. Some patients were operated upon without thyroid scan because of the ominousness of their physical findings.

All operations were performed in a standardized fashion by one of two attending surgeons or by resident surgeons under their direction. Standard collar incision and midline strap muscle separation provide access to the thyroid gland and tracheoesophageal nodes, which are carefully inspected and palpated. Suspicious nodes are examined by frozen section and, if positive or if there is direct invasion of surrounding tissue, a modified neck dissection with sternocleidomastoid muscle and spinal accessory nerve preservation is performed on the involved side. Regardless of the extent of resection required, identification and preservation of the recurrent laryngeal nerves and parathyroid glands are mandatory and painstakingly performed. In recurrent nerve involvement by tumor, vocal cord paralysis is usually evident preoperatively and the nerve is resected with the tumor. Almost always, adequate parathyroid tissue can be spared. If, however, the required dissection has removed or insulted the bulk of parathyroid tissue or its vascularity, parathyroid transplant is recommended. Biopsy proof is obtained to ensure the nature of the specimen and the remainder is minced into 1×3 mm pieces and transplanted into the sternocleidomastoid or brachioradialis muscle.

The extent of resection is dictated not only by the findings at exploration but also by the statistical findings in this patient population. Earlier, subtotal thyroidectomy (lobectomy and isthmusectomy) was performed for benign appearing pathology. However, the difficulty of securing reliable frozen section diagnosis of cancer, the high incidence of multifocal microscopic carcinoma and unsuspected carcinoma opposite the known abnormality, and our successful avoidance of significant complications have caused us recently to favor near-total or total thyroidectomy in all

Table 1. *Pathology of 112 Resected Irradiated Thyroid Glands*

	NO. OF PATIENTS	TOTAL
Benign		
Adenomata	45 (63.4%)	
Adenomata and thyroiditis	17 (23.9%)	
Atypia	9 (12.7%)	
		71 (63.3%)
Malignant		
Papillary: papillary	20 (48.8%)	
papillary-follicular	9 (22.0%)	
sclerosing	2 (4.8%)	
Follicular	10 (24.4%)	
		41 (36.7%)
		112 (100%)

these patients. The near-total approach involves leaving the slightest amount of thyroid tissue directly adjacent to the penetration of the cricothyroid membrane by the recurrent nerve.

All specimens are fixed in buffered formalin, sectioned at 5 mm intervals, and blocked and stained by conventional hematoxylin and eosin in order to assess the incidence of microscopic and multifocal carcinoma.

Results

One hundred twelve patients underwent surgery for abnormal thyroid examination and/or scan subsequent to head and neck irradiation (Table 1). Seventy-one patients (63.3 per cent) had exclusively benign pathologic findings, consisting of follicular adenomata in nearly two-thirds with thyroiditis in an additional one-fourth. Only 12.7 per cent of these patients revealed atypia. The remaining 41 patients (36.7 per cent) had carcinoma. In each patient, the tumor was well differentiated; the most common was pure papillary, with papillary-follicular and pure follicular each one-half as frequent.

In 23 patients (56.1 per cent), the tumors were associated with benign pathology, most commonly adenomata (Table 2). Nine patients (22.0 per cent) had tumors less than 0.5 cm in diameter—occult or microscopic carcinoma—and 14 (36.6 per cent) had multicentric carcinoma. Eight patients (19.5 per cent) were found to have small foci of carcinoma exclusively in the lobe opposite that which provided the indication for operation. Seventeen patients (41.5 per cent) had metastatic deposits within lymph nodes or direct invasion of tumor into trachea or other adjacent structures, but no patient had disseminated metastases.

Table 2. *Characteristics of 41 Malignant Tumors*

Associated adenomata	23 (56.1%)
Occult focus (<.5 cm)	9 (22.0%)
Multiple foci	14 (36.6%)
Tumor site opposite diagnosed site	8 (19.5%)
Metastasis to lymph nodes and/or extracapsular extension	17 (41.5%)

Table 3. *Patient Population*

	PATHOLOGY		
	Benign	Malignant	TOTAL
Male	27 (69.2%)	12 (30.8%)	39 (100.0%)
Female	44 (60.3%)	29 (39.7%)	73 (100.0%)
TOTAL	71 (63.3%)	41 (36.7%)	112 (100.0%)
Age			
Range	18 to 57 years	12 to 57 years	12 to 57 years
Average	34.0 years	30.5 years	32.7 years

These 112 patients included 39 men (34.8 per cent) and 73 women (65.2 per cent), ranging in age from 12 to 57 years, averaging 32.7 years (Table 3). It is interesting that in this group of patients females were more likely than males to have cancer and that cancer developed in younger patients than did benign disease.

The indications for irradiation included most commonly hypertrophied tonsils and adenoids, acne vulgaris, hypertrophied thymus, and various facial lesions (Table 4). The incidence of malignant change was approximately 40 per cent after irradiation for tonsillar hypertrophy or acne vulgaris, but less after treatment for thymic hypertrophy and greater after treatment for facial lesions. The interval from irradiation to diagnosis was relatively constant, averaging 24.4 years (Table 5), although there was a tendency for quicker development of malignant lesions in general, especially in males and after tonsillar irradiation.

Operations performed on these 112 patients varied from subtotal to total thyroidectomy with bilateral modified neck dissections (Table 6). Seventy-two total thyroidectomies were performed, and 17 included lymph node dissections. Only 15 patients had near-total thyroidectomies, required by recurrent nerve or parathyroid anatomy in patients thought to have benign disease. Three of these patients (20.0 per cent) had microscopic tumor found upon subserial sectioning. The remaining 25 patients underwent subtotal thyroidectomy, largely before the incidence of multifocal carcinoma was appreciated.

Table 4. *Indications for Prior Head and Neck Irradiation*

	PATHOLOGY		
CONDITION TREATED	Benign	Malignant	TOTAL
Tonsils and adenoid hypertrophy	29 (61.7%)	18 (38.3%)	47 (42.0%)
Acne vulgaris	13 (59.1%)	9 (40.9%)	22 (19.6%)
Thymus hypertrophy	13 (76.5%)	4 (23.5%)	17 (15.2%)
Facial lesions	7 (46.7%)	8 (53.3%)	15 (13.4%)
Other	5 (83.3%)	1 (16.7%)	6 (5.4%)
Unknown	4 (80.0%)	1 (20.0%)	5 (4.5%)
TOTAL	71 (63.3%)	41 (36.7%)	112 (100%)

Table 5. *Interval from Irradiation to Diagnosis*

	PATHOLOGY		
	Benign	Malignant	TOTAL
Male	26.9 years	18.9 years	24.4 years
Female	25.4 years	22.8 years	24.4 years
Target of irradiation			
Thymus	24.4 years	27.5 years	26.0 years
Tonsil	29.1 years	21.8 years	25.1 years
Face	25.1 years	23.8 years	24.5 years
TOTAL	26.0 years	21.7 years	24.4 years

Only three patients required parathyroid transplantation. One was done following a subtotal thyroidectomy for benign disease and the remaining two following total thyroidectomy and node dissection for proven carcinoma. None of these three patients suffered hypocalcemia.

Complications occurred in 18 patients, but none caused major or prolonged morbidity. Thirteen patients had temporary hypocalcemia, but no patient required treatment longer than several weeks. Three patients had temporary hoarseness that resolved by the time of discharge. One additional patient required local treatment for a superficial wound infection. There was no operative mortality. Patient follow-up has revealed no death caused by recurrent or persistent carcinoma within the follow-up period up to 13 years.

Analysis

Since our indications for surgery of the irradiated thyroid currently include abnormalities by palpation or scan, the relative accuracy of these diagnostic methods is of concern. The distribution of patients according to results of physical examination, thyroid scan, and pathologic findings (Table 7) reveals that no patient normal on both palpation and scan was operated. These patients receive suppression of thyroid stimulating hormone and are reexamined periodically by palpation and scan.

Table 6. *Procedures in 112 Patients with History of Irradiation and Abnormal Thyroid Glands*

	PATHOLOGY		
OPERATIONS	Benign	Malignant	TOTAL
Total thyroidectomy	46	26	72
without node dissection	46	9	55
with node dissection	0	17	17
Near-total thyroidectomy	12	3	15
Subtotal thyroidectomy	13	12	25
TOTAL	71	41	112

Table 7. *Correlation of Diagnostic Studies and Pathology*

EXAMINATION	NUCLEAR SCAN	PATHOLOGY Benign	Malignant	TOTAL
–	–	0	0	0
–	+	10 (71.4%)	4 (28.6%)	14 (12.5%)
+	0	2 (28.6%)	5 (71.4%)	7 (6.3%)
+	–	2 (33.3%)	4 (66.7%)	6 (5.4%)
+	+	57 (67.1%)	28 (32.9%)	85 (75.8%)
		71 (63.3%)	41 (36.7%)	112 (100.0%)

*– = negative, + = positive, and 0 = not done.

Fourteen patients (12.5 per cent) without palpable abnormalities had abnormal scans. All but one of these patients had solitary "cold" nodules, and 10 of them (71.4 per cent) had only follicular adenomata with no evidence of malignancy. The remaining four patients (28.6 per cent), including one patient with a diffusely abnormal scan, had carcinomas, each of which was microscopic, multifocal, and coexistent with multiple adenomata. One patient with a "cold" nodule had carcinoma found in the opposite lobe, and the single patient with diffusely abnormal uptake revealed foci of sclerosing carcinoma. This group of patients illustrates the inadequacy of physical examination alone and supports the use of routine scanning.

Seven patients (6.3 per cent) had palpable abnormalities that alone provided indication for surgery, so scans were omitted. Four patients had large solitary nodules and the remaining three had ominous adenopathy. These three patients and two of those with large nodules had carcinoma (71.4 per cent), whereas the remaining two patients had only adenomata. Exploration and lymph node biopsy revealed lymph node involvement in all five patients with carcinoma, necessitating lymph node dissections. The high incidence of carcinoma in this group is attributed to the high incidence of palpable significant adenopathy.

Six other patients (5.4 per cent) each had palpable discrete thyroid nodules but normal thyroid scans. Two of these patients (33.3 per cent) had only adenomata that were small and missed by Tc scans done without oblique views. The remaining four patients (66.7 per cent) had normal ^{131}I scans but were found to have carcinomas of greater diameter than 0.5 cm corresponding to the palpable abnormalities. Two of these patients required modified neck dissections because of lymph node involvement not appreciated preoperatively. These patients illustrate the limited usefulness of ^{131}I scanning, and it is conceivable but not substantiated that Tc scans in these patients might have predicted the presence of the "cold" nodules. It is clear, however, that a negative thyroid scan in the presence of a palpable nodule should not obviate the need for surgery.

Finally, the remaining 85 patients (75.9 per cent) had both palpable abnormalities and abnormal thyroid scans (Table 8). Within this group, the incidence of carcinoma was 32.9 per cent. Of these 28 patients, 18 (64.3 per cent) had palpable thyroid nodules only, eight (28.6 per cent) had palpable adenopathy with or without thyroid nodules, and the remaining

Table 8. *Correlation of Abnormal Physical Findings and Thyroid Scans in 85 Patients*

	PATHOLOGY		
	Benign	Malignant	TOTAL
Physical Examination			
Thyroid nodule only	47 (82.5%)	18 (64.3%)	65 (77.6%)
Adenopathy only	0 (0.0%)	8 (28.6%)	8 (9.4%)
Goiter	10 (17.5%)	2 (7.1%)	12 (14.0%)
TOTAL	57 (100.0%)	28 (100.0%)	85 (100.0%)
Thyroid Scan			
Cold nodule	51 (89.5%)	25 (89.3%)	76 (89.4%)
Diffuse irregularity	6 (10.5%)	3 (10.7%)	9 (10.6%)
TOTAL	57 (100.0%)	28 (100.0%)	85 (100.0%)

two (7.1 per cent) had only diffuse thyroid enlargement. Of the 57 patients with benign disease, 47 (82.5 per cent) had thyroid nodules and the remaining 10 (17.5 per cent) had diffuse thyroid enlargement. Clearly the diagnosis was made preoperatively in the eight patients with ominous adenopathy. If these patients are omitted, the 20 patients who were found to have cancer were distributed similarly to those 57 with benign disease—90 per cent versus 82.5 per cent with nodules and 10 per cent versus 17.5 per cent with goiter, respectively. The distributions of the scan results are also similar regardless of pathologic findings: 89 per cent with "cold" nodules and 11 per cent with diffuse irregularity in both benign and malignant groups.

Analysis of the entire patient series by diagnostic abnormalities revealed interesting results. In the 71 patients with physical abnormalities limited to palpable thyroid nodules, the incidence of carcinoma was 29.6 per cent; in the 14 patients with diffuse thyroid enlargement, the incidence of cancer was 21.4 per cent; and all 13 patients with ominous adenopathy had cancer. Thus, the total incidence of cancer in patients with abnormal physical examinations was 37.8 per cent. In 89 patients with discrete "cold" nodules on thyroid scan, the incidence of cancer was 31.5 per cent, and in 10 patients with diffusely abnormal scans, the incidence of cancer was 40.0 per cent. Thus, the total incidence of cancer in patients with abnormal thyroid scans was 32.3 per cent.

CONCLUSION

In light of our own experience, the experience of others in the current literature, and the demographic, histopathologic, and natural historical characteristics of irradiated thyroid disease, we propose the following approach to patients with a history of head and neck irradiation.

Evaluation is carried out with a careful history, physical examination, and thyroid scan using ^{99m}technetium pertechnetate with scintillation camera and pinhole collimator. Thyroid function tests are performed

as indicated but generally do not influence the therapeutic outcome. Patients normal or equivocal on both physical examination and scan are given thyroid suppression therapy and followed clinically at frequent intervals. Patients with palpable abnormalities including nodularity, diffuse enlargement, and suspicious cervical adenopathy or those with abnormal scans suggestive of nodular disease, even with normal physical findings, are advised to have an operation. These indications are warranted by the high incidence of cancer in irradiated glands with palpable or scan-proven abnormalities. The sensitivity and accuracy of the Tc scan we employ justify the acceptance of scan-proven nodules in patients normal on clinical examination as sufficient indication for surgery. Such patients have been shown to have as high an incidence of carcinoma as those with palpable disease.

When surgery is indicated, total or near-total thyroidectomy is carried out with meticulous attention to preservation of recurrent nerve and parathyroid function. When it appears that the dissection will likely jeopardize the bulk of parathyroid tissue, we transplant biopsy-proven parathyroid tissue into the sternocleidomastoid or brachioradialis muscle. If initial inspection of cervical nodes suggests metastatic disease and subsequent biopsy confirms this, modified neck dissection as described above is carried out.

We feel this more extensive surgical approach is appropriate because of the high incidence of multicentric, bilobar, and microscopic cancer, the high incidence of cancer associated with benign disease and the frequency with which it appears in areas other than those of the clinically detectable lesions, the difficulty of frozen section diagnosis, the high incidence of recurrence following less extensive surgery, and the improved results of ^{131}I therapy for residual disease when all normal thyroid tissue is gone. Furthermore, while we agree that the long-term clinical significance of occult post-irradiation thyroid cancer is not known, we recognize that the population we are treating is generally young, and thus we are less willing to permit occult carcinoma to be left behind where it will have a longer time to possibly become clinically significant; post-irradiation thyroid cancer has the capacity to cause significant local disease, distant metastases and death; and we and others[35, 43, 60] are able to perform total or near-total thyroidectomies on these patients with little or no significant morbidity and no mortality. Thus, the benefit derived from the more extensive procedure outweighs the minimal risk incurred.

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Radiation Exposure and the Simultaneous Occurrence of Primary Hyperparathyroidism and Thyroid Nodules

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Primary hyperparathyroidism in association with thyroid carcinoma was first observed in four patients in 1956.[28] Subsequent reports indicate that as many as 5 to 11 per cent of patients with primary hyperparathyroidism have simultaneous thyroid carcinomas.[9, 14, 16–19, 22, 29, 38, 43] When non-neoplastic thyroid diseases are included, the incidence of clinically detectable thyroid disorders in patients with primary hyperparathyroidism rises to a range of 31 to 50 per cent.[9, 11, 14, 16, 18, 22, 29, 31, 41] No entirely satisfactory explanation has been given for this phenomenon.

The association of exposure of the head and neck to radiation and the later development of neoplasms has been extensively discussed in the last 25 years. It is best recognized in the pathogenesis of thyroid carcinomas.[6, 30, 33] The association has also been made with other tumors arising in the head and neck, including cutaneous cancers,[25] tumors of major salivary glands,[3, 13, 16, 26] and some brain tumors.[12, 26, 36] It has been suggested[36] and disputed in the pathogenesis of leukemias.[26]

More recently, clinical and experimental data suggesting that radiation exposure may be a factor in the development of primary hyperparathyroidism have been reported. In 1975, the first report describing a patient with hyperparathyroidism and the history of exposure to radiation of the head and neck was published.[35] Evaluation of several large series of patients with proven primary hyperparathyroidism indicate that 14 to 30 per cent had previous exposure.[5, 31, 40] Several authors have emphasized

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that the percentage of patients with histories of radiation exposure may be minimal, because of the long latent period between exposure and the clinical appearance of parathyroid disease. LiVolsi and colleagues, however, in a retrospective study of a large series of patients with parathyroid adenomas, could find no evidence to support the concept that radiation was a factor in the pathogenesis of parathyroid disease.[24]

This report, stimulated by the conflicting clinical evidence, focuses on 58 patients proved to have concomitant thyroid disease and primary hyperparathyroidism. This study was limited to this group, selected from 425 patients with primary hyperparathyroidism, because of the recognized association between thyroid nodules and previous irradiation and the logistic difficulties in obtaining an accurate retrospective history of radiation exposure in any large group of adult patients.

MATERIALS AND METHODS

In a 12-year period (1965 to 1976), 425 patients with primary hyperparathyroidism underwent operations at the University of Michigan Medical Center. A preliminary review of the pathologic material from these patients revealed that 58 were proven to have both parathyroid and thyroid diseases that were evaluated histologically. The criteria used to select patients to be included in this study were that both parathyroid and thyroid diseases had to be grossly obvious to the surgeon at the time of operation and sufficient tissue had to be removed for adequate microscopic examination. Five patients with bilateral medullary carcinomas of the thyroid and parathyroid hyerplasia were excluded, as they were considered to have multiple endocrine adenomatosis type II syndromes known to be of genetic origin. The clinical records of the 53 remaining patients were carefully reviewed. Some patients, whose charts contained insufficient information concerning previous exposure to head and neck irradiation, were personally contacted. When possible, specific information was obtained about the actual dose of radiation administered to the head and neck, although in most cases this information was unavailable. The pathologic classification of the thyroid diseases was simple because only well recognized diseases were found in this group of patients.

The differentiation of parathyroid hyperplasia from parathyroid adenoma, however, was more difficult. The presence of multiglandular parathyroid disease, in our opinion, indicates primary parathyroid hyperplasia, whereas presence of one hyperplastic gland with all other parathyroid glands normal is interpreted as an adenoma. It is our operative policy in patients with primary hyperparathyroidism to evaluate all four glands grossly before determining the extent of resection. If it appears that an adenoma or a single gland disease is present, the enlarged gland is removed and biopsy specimens of two or three of the remaining glands are taken. All specimens are submitted for examination by frozen sections. If multiglandular disease is present, 3½ parathyroid glands are removed. In our experience, multiglandular disease involving less than four glands has been very unusual. In a few patients included in this

study, only one enlarged hyperplastic parathyroid gland was removed, usually in association with a description of the remaining parathyroid glands being grossly normal. When follow-up studies revealed no recurrence or persistence of hypercalcemia, a diagnosis of "adenoma" was accepted.

RESULTS

There were 42 women and 11 men with concomitant thyroid and parathyroid diseases. The average age of the women was 50 years and was 40 years for the men (range 15 to 76 years).

All 53 patients were hypercalcemic as determined by at least one elevated serum calcium determination done prior to neck exploration. The presenting symptoms in 30 patients (57 per cent) were those of hyperparathyroidism and included weakness, fatigue, polyuria, renal stone disease, emotional lability, anorexia, abdominal pain, arthralgias, and bone pain. Three patients had symptoms directly related to their thyroid disease: two with Grave's thyrotoxicosis, and one with an enlarging painful thyroid nodule. Nine of 20 asymptomatic patients (38 per cent) were found to be hypercalcemic after routine test panel serum calcium determinations, whereas 10 patients with asymptomatic thyroid nodules were found to have elevated serum calcium levels after those studies were performed as part of their routine evaluation. One patient who had a thyroid scintiscan at his request was found to have a "cold" defect in his thyroid gland.

The primary indication for neck exploration was the diagnosis of primary hyperparathyroidism in 38 (72 per cent) of this group of 53 patients. At operation, an abnormality was found in the thyroid gland and the lesion removed by total or partial lobectomy. In most cases this was done because the gross findings were suspicious for thyroid carcinoma. One unusual patient, presenting with a parotid mass and a serum calcium level of 14 mg per dl, was found to have a nodular goiter, parathyroid adenoma, and a mucoepidermoid carcinoma of the parotid gland.

In 15 patients (28 per cent), thyroid disease was considered to be the primary indication for operation, although in all but one, exploration of the parathyroid glands was also considered to be indicated. This group of patients all had asymptomatic hyperparathyroidism and serum calcium levels ranging from 11 to 11.5 mg per dl. One patient, explored for a solitary thyroid nodule, which was a follicular carcinoma, was discovered to have a parathyroid adenoma measuring 1 × 1 cm which was excised. Her preoperative serum calcium level was found, in retrospect, to be elevated.

The pathologic changes found in the thyroid glands of these 53 patients included 33 nodular goiters, 7 Hashimoto's disease, 3 follicular carcinomas, and 10 papillary carcinomas. Of the 10 papillary carcinomas, only two were larger than 1 cm and clinically apparent before operations. The remainder were less than 1 cm in size and were discovered at the time of parathyroid exploration.

A history of exposure of the head and neck to radiation was recorded in the charts of 13 patients and determined from subsequent interviews in 5 additional patients. Thus, although 34 per cent of patients were eventually determined to have been exposed to head and neck irradiation, there was no indication that a history of radiation had been obtained in 75 per cent of the case records. It also became clear that more than half of all patients responding negatively to the question of radiation exposure during infancy or childhood were tentative or inconclusive in their answers. Several patients were reclassified and placed in the positive group after consultation with relatives, family physicians, or review of old records.

The mean interval between the exposure to radiation and the detection of any thyroid or parathyroid disease (latent period) was 29 years. The shortest interval was 7 years, and the longest, 51 years. The mean age of patients irradiated was 21 years (range from 4 to 47 years). The mean latent period for the 3 men in this series was only 20 years in contrast to the mean latent period of 33 years for the 15 women. None of these patients had irradiation to the thymus. The most common indication for irradiation was the treatment of acne or other benign skin disease (8 patients). Other indications included thyrotoxicosis, sinusitis, cervical adenopathy, and breast carcinoma. One patient, treated for Grave's disease by the topical application of radium in 1939, developed a thyroid nodule 20 years later. During the next 17 years, the nodule slowly enlarged and measured 10×10 cm when she was explored in 1976. She was found to have a large colloid nodule, in the center of which was a papillary carcinoma 5×5 cm in size. In addition, she had a parathyroid adenoma involving the right superior gland. Another patient had a subtotal thyroidectomy for Grave's disease at 16 years of age. Because of recurrent thyrotoxicosis, her thyroid gland was treated with external irradiation at 21 years of age. When evaluated 26 years later because of hypertension and headaches, although euthyroid, she was hypercalcemic. Nodular Hashimoto's disease of the remaining right thyroid lobe remnant and a parathyroid adenoma were found at operation. The patient who also had a parotid tumor was 59 years of age. She had received irradiation to the head and neck for acne 37 years earlier. Twenty years later a right thyroid lobectomy was performed for a benign colloid nodule. When seen in 1977, she had a parotid mass, a serum calcium of 14.6 mg per dl, and nodules in her remaining left thyroid lobe. She was found to have a mucoepidermoid carcinoma of the parotid gland, colloid nodules in her remaining thyroid gland, and a large parathyroid adenoma. The youngest patient treated with radiation was four years of age when he received 1125 rads to the ethmoid and maxillary sinuses for the treatment of purulent sinusitis. He developed parathyroid hyperplasia and a nodular goiter 25 years later. The patient with the shortest interval between irradiation and the development of hypercalcemia and a thyroid nodule had received 4000 rads to the mediastinum and supraclavicular areas as adjunctive therapy for bilateral carcinomas of the breast seven years previously. She was found to have a follicular carcinoma of the thyroid, in addition to a parathyroid adenoma.

The majority of the thyroid carcinomas (9 of 13 patients) were found in the group of patients previously exposed to radiation. However, six of

the nine carcinomas were smaller than 1.5 cm, and were not clinically detectable. Two patients with occult lesions had multiple foci of papillary carcinoma within their thyroid glands. The remaining three patients had larger lesions which were clinically apparent before operation.

There were four thyroid carcinomas found in the "nonirradiated" group. Two of the three follicular carcinomas were found in this group of patients. The papillary lesions in the nonirradiated group were both occult. Seven of the eight patients with Hashimoto's disease were also in this group. The remaining patients in both groups had nontoxic nodular goiters.

Seven of the nine patients with thyroid carcinomas in the "irradiated" group had parathyroid "adenomas," as did all four patients with thyroid carcinomas in the "nonirradiated" group. In the entire group, there were 37 patients (70 per cent) with "adenomas," and 16 (30 per cent) with hyperplastic parathyroid glands.

These results may be summarized as follows. Eighteen of 53 (34 per cent) patients with simultaneous thyroid and parathyroid disease had been exposed to irradiation of the head and neck. This is believed to be a minimal figure. In 9 of 18 patients (50 per cent) with primary hyperparathyroidism who were previously exposed to radiation, thyroid carcinomas occurred simultaneously. Only 4 of 35 patients (12 per cent) with hyperparathyroidism with no history of radiation exposure had malignant tumors of the thyroid gland. Of those patients with simultaneous papillary thyroid carcinoma and hyperparathyroidism, 80 per cent had previous irradiation to the head or neck. Only one of three patients with follicular carcinoma had a similar history.

DISCUSSION

Several inferences may be drawn from the preceding data. Radiation to the head, neck, and upper chest may be a factor in the development of parathyroid disease and may account for the significant number of patients with primary hyperparathyroidism occurring simultaneously with thyroid carcinomas. There is some experimental and accumulating circumstantial clinical evidence to support these views.

Lindsay's report on radiation-induced thyroid neoplasia included a rat treated with ^{131}I which developed a parathyroid adenoma.[20] He then varied the dose of radiation in later experiments to induce thyroid neoplasia. An interesting finding was the induction of parathyroid hyperplasia or adenomas in 41 per cent of the exposed rats, as compared with 19 per cent in the control group. This was pursued further by the induction of thyroid carcinomas in female rats with a single low dose of ^{131}I. Results of examinations of the parathyroid glands, however, were not as convincing, as 47 per cent of the irradiated females had parathyroid hyperplasia or adenomas, compared with 42 per cent of those in the control group.[21] Warren concluded that radiation could induce parathyroid neoplasia in the rat.[45] In his experiments, two young rats were joined as a parabiont pair. One rat received 1000 rads. After 18 months, only the irradiated rats

developed invasive parathyroid neoplasms. In 1972, Berdjiis, using a large number of experimental animals exposed to varying doses of radiation, sought evidence linking irradiation and parathyroid disease.[4] In one experiment,8 per cent of irradiated rats developed parathyroid tumors, compared with none in 160 control rats of the same species. He divided the radiation-induced changes in the parathyroid glands into early and late phases. Included as late manifestations were disordered architecture, proliferative centers, hyperplasias, adenomas, and carcinomas.[37] Most recently, Triggs and Williams added their observations on the effects of irradiation of the parathyroid glands, again as a side effect of experiments done on radiation-induced thyroid disease.[42] Adenomas were found in 61 per cent of young rats treated with ^{131}I as opposed to none in the controls. They surmised that irradiation could induce parathyroid tumors in man as well.

Evidence of the long-term effects of irradiation on the human parathyroid glands has been scarce and inconclusive. The primary interest in irradiation of the parathyroid glands 50 years ago was as a therapeutic modality for advanced hyperparathyroidism. It had been shown by Walters et al. in 1931 that radiation exposure of the parathyroids in normal dogs resulted in a slight hyperplasia of the glands, but no increase in the serum calcium levels.[44] From clinical experience, it was known that exposure of the parathyroids to huge doses of radium and x-rays in the treatment of cervical malignancies did not cause symptoms of tetany. Nevertheless, it was considered likely that hyperplastic parathyroids, or adenomas, would be more radiosensitive. The successful treatment of osteitis fibrosis cystica by cervical irradiation was soon reported. In 1934, irradiation of the parathyroid glands was proposed as the therapy of choice when surgical operations were contraindicated or when a neck exploration failed to produce a cure.[7] Further interest in the use of irradiation as a definitive treatment for primary hyperparathyroidism diminished as improved surgical techniques and experience developed. With the introduction of ^{131}I as a therapy for both hyperthyroidism and differentiated thyroid carcinomas, some concern developed about the possible occurrence of hypoparathyroidism.[1] Most studies have shown that the parathyroid glands are rarely affected, at least functionally, by the beta irradiation concentrated in the thyroid glands of patients receiving ^{131}I. Eipe, in 1968, reported a case of hypoparathyroidism induced by ^{131}I and noted three others previously reported in the literature.[8] At that time, there were no reports of late histologic changes occurring in the parathyroid glands of patients previously irradiated with either ^{131}I or external radiation.

Rosen in 1975 was the first to emphasize the possible association of irradiation and parathyroid gland neoplasia.[35] His patient, irradiated at age 17 years for facial hirsutism, developed malignant skin lesions, a salivary gland tumor, and a parathyroid adenoma 40 years later. Kairaluoma, in reporting on two patients with simultaneous parathyroid adenomas and papillary carcinomas, noted that one had received irradiation for tuberculous cervical adenitis.[14] While the importance of such a history was acknowledged in the etiology of the thyroid carcinoma, it was dismissed as a factor in the development of parathyroid tumors. Exposure

to radiation in adults was considered to be of "minor importance." The first large series of patients in which the development of hyperparathyroidism was considered to be a late complication of neck irradiation was reported by Tisell et al. from Göteborg, Sweden.[40] They determined that 14 per cent of 170 patients with primary hyperparathyroidism had received from 200 to 3000 rads to the neck an average of 42 years earlier. In a similar study of 89 patients with hyperparathyroidism, Prinz et al. found that 30 per cent had been exposed to neck irradiation. The average latent period was 30 years.[31] Block, in discussing this paper, noted that 18 per cent of his last 100 patients with hyperparathyroidism had received ionizing radiation to the head or neck.[5] Again, a long latent period before the development of hyperparathyroidism was noted. Perhaps related to the prolonged latent period, only a few cases of hyperparathyroidism have been uncovered in large series of patients screened for possible thyroid neoplasms because of neck irradiation in infancy or childhood. Kaplan found no patients with primary hyperparathyroidism in a group of 500 patients evaluated because of known irradiation during childhood.[15] However, the average age of patients being evaluated in most screening programs for possible thyroid neoplasms is approximately 30 years of age, whereas the average age of the recently reported patients with possible radiation-associated hyperparathyroidism was 50 years.

The most conclusive study relating irradiation of the neck to the subsequent development of hyperparathyroidism was recently reported by Tisell and colleagues.[41] Their subjects had all been treated with x-rays for tuberculous cervical adenitis between 1930 and 1946 and were the first 100 consecutive individuals who responded to a request to return for follow-up studies. Each patient was carefully evaluated and examined and then had both thyroid and parathyroid gland function studies performed. Those patients with elevated serum calcium levels or thyroid nodules were hospitalized for further evaluation or neck explorations. From the detailed Swedish record system, it was possible to calculate estimated absorbed doses of radiation to the parathyroid glands in each patient. At follow-up, 10 patients were found to be hypercalcemic. Six with signs and symptoms compatible with primary hyperparathyroidism had neck explorations. The diagnosis of parathyroid adenoma or hyperplasia was confirmed in each. Two other patients had previously had parathyroid adenomas excised. Three additional patients, explored because of the presence of thyroid nodules, had abnormal parathyroids excised. Two of them had concomitant papillary carcinomas of the thyroid. Thus, 11 of 100 patients were proved to have developed parathyroid adenomas or hyperplasias, and four additional patients had asymptomatic hypercalcemia. In all patients with abnormal parathyroid glands, simultaneous thyroid disease was found. It was estimated that the mean absorbed radiation dose in the parathyroid glands varied from 75 to 2200 rads. Hyperparathyroidism did not occur in individuals exposed to doses under 300 rads, but was found in 3 of 39 whose doses ranged from 300 to 600 rads. From the group of 28 patients receiving 600 to 1200 rads, four developed hyperparathyroidism. Four of six individuals receiving doses exceeding 1200 rads developed hyperparathyroidism.

The extremely high incidence of hyperparathyroidism in this series of patients with neck irradiation compares with an incidence of 1 in 834 patients found in outpatient testing, and indicates a causal connection between radiation treatment and the development of hyperparathyroidism. A further indication of this correlation is the fact that hyperparathyroidism was more frequent in patients most heavily exposed to radiation. The finding that 36 of the 100 subjects were either completely unaware or had forgotten that they had received radiation therapy is disconcerting but consistent with our own experience in obtaining such histories. More than half of the patients were 20 years of age or older when radiation was administered. All of the patients in this series were older than 40 years of age when the diagnosis of hyperparathyroidism was established. The average time between radiation exposure and the diagnosis of hyperparathyroidism was 38 years. From this experience, Tisell concluded that hyperparathyroidism may be a more common late complication of neck radiotherapy than thyroid carcinoma.

The association of primary hyperparathyroidism with nonmedullary thyroid carcinomas has puzzled clinicians since Ogburn and Clack's initial report of four patients in 1956.[28] They attributed the association to coincidence. During the next 20 years, approximately 100 cases were reported in a total of 1500 patients with primary hyperparathyroidism (6.7 per cent).[9, 14, 16–19, 22, 29, 38, 43] A history of irradiation exposure was not mentioned in any of these reports. Ellenberg et al. in 1962 found the association sufficiently frequent to suggest that it should be considered to be a third type of multiple endocrine syndrome.[9] However, there is no evidence of a genetic basis for the association of nonmedullary thyroid cancer and hyperparathyroidism, nor have there been any reports of its familial occurrence.

A few investigators, in noting an incidence of benign and malignant thyroid disease in 37 to 50 per cent of patients with primary hyperparathyroidism, have addressed the problem of etiology.[9, 11, 18, 22, 28, 29, 43] They have usually referred to early investigations showing that calcium is a goitrogen. Taylor, in 1946, found that calcium carbonate added to the diet exerts a goitrogenic effect in the rat by inhibiting the synthesis of thyroxin and that this effect was enhanced if the animal was on a low iodine diet.[39] If hypercalcemia per se caused a similar effect in man, goiters or perhaps thyroid carcinomas induced by TSH stimulation might result in patients with chronic hyperparathyroidism. This hypothesis would require that hyperparathyroidism developed first and the thyroid disease occurred as a consequence of subsequent thyroid hormone deficiency. Neither condition has been proved in man. All of our patients with simultaneous hyperparathyroidism and thyroid carcinomas were euthyroid and four had normal TSH levels. Although other causes of parathyroid adenomas and hyperplasias have been suggested, including the ingestion of thiazides, none has been associated with the simultaneous occurrence of parathyroid and thyroid disease. The effect of excessive calcitonin production in response to chronic hypercalcemia has also been considered. Several reports indicate that C-cell hyperplasia may be found in the thyroid glands of a third or more of patients with primary

hyperparathyroidism.[23, 46] The significance of this finding is currently unknown, however, as there is no evidence that the incidence of sporadic medullary carcinoma is increased in patients with hyperparathyroidism, or that calcitonin induces other thyroid gland neoplasms.

None of the preceding explanations is entirely satisfactory. Although radiation exposure appears to be the most commonly associated factor in patients with hyperparathyroidism and simultaneous thyroid carcinomas, some patients with both diseases have not had head or neck irradiation. One explanation is the only recently recognized high incidence of small papillary carcinomas in the general population, as determined from autopsy studies.[27] Some of these can be detected by careful direct palpation of the thyroid gland. We have seen two additional patients during the past year with papillary thyroid carcinomas found at neck explorations for hyperparathyroidism in whom there was definitely no history of previous irradiation. LiVolsi et al. in a retrospective study of 40 patients with simultaneous thyroid carcinomas and parathyroid adenomas were able to obtain a history of radiation to the head or neck in only 1 of 32 (2.5 per cent) patients in which this information was apparently available.[24] Notwithstanding the known difficulties in obtaining accurate irradiation information in a retrospective study of this type, it appears likely that other undetermined etiologic factors may be involved in the simultaneous appearance of hyperparathyroidism and thyroid carcinomas in some patients.

SUMMARY

The occurrence of primary hyperparathyroidism and simultaneous nonmedullary thyroid carcinomas is unexpectedly high and ranges from 2.5 to 11 per cent. Exposure of the neck to ionizing radiation has been established as an etiologic factor in the development of thyroid carcinomas and has recently been implicated as a factor in the pathogenesis of primary hyperparathyroidism. Because of the difficulties in obtaining accurate information about radiation exposure in a large series of patients with primary hyperparathyroidism, attention was focused on 53 patients who had simultaneous thyroid and parathyroid diseases, extracted from a group of 425 patients with proven primary hyperparathyroidism. The incidence of simultaneous nonmedullary thyroid cancer found in the larger group was 3 per cent. Thirty-four per cent with simultaneous benign and malignant thyroid disease had been previously exposed to head and neck irradiation. The mean latent period between exposure and the clinical recognition of parathyroid disease was 30 years. Fifty per cent of the 18 patients with hyperparathyroidism who were previously irradiated had simultaneous thyroid carcinomas. Of those patients having simultaneous papillary thyroid carcinomas and hyperparathyroidism, 80 per cent had previous irradiation exposure to the head or neck.

There is both experimental and clinical evidence suggesting that radiation may be a factor in the etiology of both thyroid carcinomas and primary hyperparathyroidism. A careful history of radiation exposure

should be obtained in all patients being evaluated for hyperparathyroidism, as well as in those with possible thyroid carcinomas. The thyroid gland should be carefully evaluated in all patients before and during neck explorations for hyperparathyroidism. Because the latent period between irradiation exposure and appearance of hyperparathyroidism may be as long as 50 years, periodic reevaluation of serum calcium levels in patients seen in thyroid cancer screening programs will be necessary to determine the incidence of hyperparathyroidism as a late complication of head and neck irradiation.

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Parathyroid Surgery

How Many Glands Should Be Excised? Is There Still A Controversy?

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There has been a controversy about how much parathyroid tissue to remove. Some surgeons have favored subtotal resection of the parathyroid glands in all cases. Others have advocated removal of the adenoma only and, in primary or familial hyperplasia or multiple endocrine adenomatosis syndrome, leaving enough tissue to avoid tetany. However, a review of the subject indicates that a controversy no longer exists. The purpose of this article is to report that resolution of the controversy on the extent of parathyroid gland resection in primary hyperparathyroidism is an already published conclusion.

HISTORICAL DEVELOPMENT

For 45 years after Mandl's first parathyroid operation in 1925, there was little discussion or controversy about the extent of resection of the parathyroid gland in primary hyperparathyroidism. Overt clinical symptoms and pathologic findings confirmed the diagnosis in most patients; few patients with hypercalcemia were asymptomatic. A single, large adenoma was removed from most patients, and when calcium levels returned to normal postoperatively, the patient was considered to be cured.

Cope in 1958 described primary hyperplasia of the parathyroid glands and advocated removal of three glands with preservation of a part of the fourth.[7]

In the late 1960s, because of the availability of the automated multichannel analysers, which included serum calcium determinations, the number of patients screened for hypercalcemia greatly increased. As a result, many cases were found around the world. At many centers, sur-

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geons with an interest in parathyroid surgery rapidly accumulated large series of patients with hyperparathyroidism. They reported extensively on their individual series, especially their own techniques. Special emphasis was placed on persisting hypercalcemia or failure of the primary operation to restore a normal serum calcium level. It was found that identification of all four glands minimized persisting hypercalcemia by eliminating any overlooked grossly abnormal glands. To confirm the identification of all four glands, many surgeons performed biopsies and the pathologists became confused because light and electron microscopy, which may show hyperplasia, frequently did not reveal enlargement or hyperfunction of the glands. Edis found that the incidence of hyperplasia increased 30-fold when the greater number of glands were submitted for pathologic study at the Mayo Clinic.[8] Our experience has been similar.[9] It should be remembered that there is still considerable confusion in the interpretation of parathyroid pathology. Kay, a pathologist, believes that the experienced surgeon is best able to differentiate between hyperplasia and adenoma at operation.[11]

From the historical standpoint, it was the rapid rise in number of cases and confusion as to histopathology, and a desire to avoid persisting and recurrent hypercalcemia that made some surgeons develop a more radical procedure for excision of parathyroid glands variously referred to as the near total, subtotal, and liberal approaches.

THE CONTROVERSY

Block, in 1967, felt that the prevalence of multiple parathyroid gland involvement, the discrepancy between gross histologic and clinical findings, and the difficulties in interpretation of biopsy specimens favored a policy of routine subtotal parathyroidectomy.[2]

Paloyan, in 1969, described near total parathyroidectomy.[15] This procedure was suggested to avoid recurrent and persisting hypercalcemia and to allow for an increasing incidence of hyperplasia. At that time, he suggested that for near total parathyroidectomy, three and one-half glands should be excised, leaving 30 to 50 mg of a well vascularized remnant.

To reduce the number of recurrences, Bruining[3] attempted subtotal parathyroidectomy in 11 patients.

Because of an increasing incidence of hyperplasia and disenchantment with the previous rates of recurrent hypercalcemia at the Barnes Hospital in St. Louis, Haff and Ballinger[10] in 1970 selected routine subtotal parathyroidectomy.

Edis reported the liberal policy of parathyroid resection for surgeon "B" at the Mayo Clinic.[8] This consisted of identification of all four glands wherever possible, routinely removing at least two, and removing three and one-half glands whenever more than one gland was enlarged. Sur-

geon "B" also freely performed biopsies to confirm normal parathyroid glands.

Many surgeons opposed these more radical approaches. They argued that:

Identification of all glands with removal of only grossly abnormal tissue would result in minimal recurrence.

Gross gland enlargement of primary hyperplasia in primary hyperparathyroidism was not occurring more frequently.

The incidence of hypoparathyroidism would be unacceptably high if the more radical procedures were recommended and literally and liberally followed.

These arguments have been studied by Clark.[5, 6]

RESOLUTION OF THE CONTROVERSY

Block, in 1974, revised his policy of routine subtotal parathyroidectomy in favor of individualization of the extent of parathyroidectomy.[1] Factors that led to his abandoning routine subtotal parathyroidectomy were a stable incidence of hyperplasia in 20 per cent of his patients, and a higher proportion of patients incurring permanent hypoparathyroidism following subtotal resection than the proportion of patients incurring recurrent hypercalcemia following selective removal of abnormal glands. He also foresaw a still higher rate of permanent hypoparathyroidism if subtotal parathyroidectomy became routine practice.

Bruining reported a 37 per cent incidence of severe, prolonged hypocalcemia following prophylactic subtotal parathyroidectomy compared with 1.2 per cent when only enlarged glands were removed.[4] He felt that these data contraindicated removal of normal glands.

Edis found that the liberal resection technique of surgeon "B" at the Mayo Clinic resulted in symptomatic hypocalcemia in 24 per cent of patients compared with 2 per cent when the same surgeon used a conservative approach.[8] The liberal approach did not produce a higher cure rate, and the Mayo Clinic now prefers the conservative approach.

Paloyan has perhaps taken the brunt of criticism from the conservative surgeons, but careful examination of the evolution of his stated technique of resection over the past nine years shows that his method is now in agreement with a more conservative approach. In his first report in 1969[15] he spoke of "near total parathyroidectomy," leaving only 30 to 50 mg of viable parathyroid tissue and excising three and one-half glands. His most recent publications of 1976 and 1977 clearly avoid any mention of near total parathyroidectomy, and the amount of tissue he prefers to leave as a viable remnant has doubled and even tripled to 100 to 150 mg. Commenting in *Controversies in Surgery*,[13] Paloyan states that each gland ordinarily weighs 35 mg, and that for normal parathyroid function in an adult 70 to 100 mg of tissue is required; 100 to 150 mg is needed for the young and elderly. This clearly requires leaving two to three glands. Paloyan

further states, "given a patient with a specific set of clinical and histopathologic findings, most endocrine surgeons today would perform essentially the same operation, no matter with which side of the controversy they allied themselves."

This policy was further emphasized by Paloyan in the same year in his discussion of Clark's paper in which he reemphasized saving halves of two glands and in some cases three glands and autotransplantation of parts of an adenoma.[12] The latter is hardly a near total parathyroidectomy. He concludes again with, "given the same patient and the same situation, Dr. Clark and most of us would do the same operation."

Paloyan's policy of leaving several multiple well vascularized gland segments was recently confirmed by his choice of leaving preferably two and sometimes three well-vascularized remnants weighing 75 to 100 mg.[13] In 166 patients, he has had but two with permanent tetany and no recurrences. Although Paloyan's surgical results have been excellent, his writings have evolved to recommend individualization of the treatment of each patient.

CONCLUSION

The general consensus of surgeons is to identify, when possible, all four parathyroid glands. Biopsy confirmation is optional.

For patients with three glands of normal size and one enlarged adenomatous gland, the enlarged gland is excised.

For patients with more than one enlarged gland owing to primary hyperplasia, familial hyperplasia, a multiple endocrine adenomatosis syndrome, or several adenomas, a subtotal parathyroidectomy is performed. Chances of hypocalcemia with subtotal parathyroidectomy may be reduced by autotransplantation or cryopreservation for later autotransplantation if necessary. Complete removal of normal glands is discouraged. Normal glands do not cause persistent or recurrent hypercalcemia.

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Prevention and Management of Complications Associated with Thyroid and Parathyroid Surgery

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Although there is considerable potential for complications with thyroid and parathyroid operations, they are uncommon when the surgeon is well versed in all aspects of thyroid and parathyroid physiology and pathology and is thoroughly familiar with the anatomy of the neck. The circumstances under which complications are most likely to occur include definitive surgery for malignant disease (for example, the vocal cord paralysis that results from sacrifice of a segment of involved recurrent laryngeal nerve) and during reoperative neck surgery when scarring and bleeding combine to distort the anatomy and obscure the operative field. Frozen-section histologic diagnosis is also a necessary prerequisite for the safe conduct of this type of surgery. Knowing the exact nature of the lesion and its biologic behavior means that the surgeon can tailor the operation for optimal management. Undertreatment or overtreatment exposes the patient to problems that can lead to complications or even mortality.

RARE COMPLICATIONS

Mortality from thyroid or parathyroid surgery almost never occurs today. Even before the turn of the century, without the benefit of blood transfusion, antibiotics, or endotracheal anesthesia, Theodor Kocher was able to perform thousands of thyroidectomies (often for huge goiters) with a mortality of less than 1 per cent. In 1917, at the conclusion of his long and illustrious career and several weeks before his death at age 76, Kocher reported on approximately 5000 thyroid operations performed with a mortality of 0.5 per cent.[4] This is a truly remarkable achievement, given that just a few decades before, the mortality for thyroidectomy approached 50 per cent. At that time, according to Becker,[4] "the majority opinion in international surgical circles was that the operation was never

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justified." Kocher's surgical contribution was to standardize and perfect the operation of thyroid lobectomy. He rendered thyroid surgery safe, and for this great work he was awarded the Nobel Prize for Medicine and Physiology in 1909—the first and only surgeon ever to win the Prize for purely clinical exploits.

The Kocher legacy was inherited in the United States by a number of gifted surgeons—among them C. H. Mayo, Halsted, Crile, Oschner, and Lahey. During the first two decades of this century, thyroidectomy was a common operation, especially in the midwestern goiter belt. At the Mayo Clinic, for example, some 30,628 thyroid operations were performed from 1892 through 1925.[17] During the year 1924 alone, 1928 thyroid resections were performed with but 10 surgical deaths, for a mortality of 0.5 per cent. This impressively low surgical mortality was attained despite the fact that more than half of these operations were performed for toxic exophthalmic goiter. Only a few years before, the mortality for thyroidectomy in such cases was at least 5 per cent because of the frequent occurrence of postoperative *thyroid crisis*. As Pemberton and Haines, Mayo physicians of that era, described it:

> Often, within a few hours after the goiter had been resected successfully, an acute explosive reaction would follow, characterized by extreme tachycardia, high temperature, nausea and vomiting, marked restlessness and prostration, mental stimulation or delirium and frequently coma; often death supervened within from twelve to forty-eight hours.[24]

It was in this setting that Henry Plummer, in 1923,[27] established the value of administering iodine solution to patients with Graves' disease in preparation for surgery. With this one imaginative step, the problem of postoperative thyroid crisis was essentially eliminated once and for all and the mortality for thyroidectomy in these cases fell to less than 1 per cent. In the years since Plummer's discovery, the risk of thyroidectomy for Graves' disease has been diminished even further by the use of antithyroid drugs and propranolol (Inderal) in the preparation of unusually toxic patients. We have continued to use Lugol's iodine solution (10 drops, three times daily, for 7 to 10 days) at the Mayo Clinic as the standard preparation for surgery in patients with Graves' disease. Thyroid crisis as a complication of thyroidectomy today is entirely preventable.

It has been customary in discussions of this type to emphasize the perils of *postoperative hemorrhage with airway obstruction*, but the problem should rarely, if ever, arise. It should hardly be necessary to remind the modern-day surgeon to use meticulous hemostasis and careful dissection technique or to use finger pressure to control accidental major venous hemorrhage. There is, however, perhaps one useful suggestion to help in minimizing operative bleeding in the neck which may not be universally well known, and that is to position the patient in a 30° head-up position. Contrary to popular belief, reducing the venous pressure in this way does not expose the patient to an increased risk of *air embolism*, provided that general anesthesia with endotracheal intubation and controlled ventilation is employed to maintain positive intrathoracic pressure in all phases of respiration. Before closing the neck, it is a good idea to have the anesthesiologist suction the trachea to stimulate a cough reflex. This momentarily increases the venous pressure in the neck to fill collapsed veins, and any untied vessels will immediately be apparent at this time.

The rare case of postoperative bleeding will usually be heralded by pain and excessive bloody drainage through the skin incision or via any drains that may have been used. Once recognized, an expanding hematoma should be evacuated by reopening the wound, preferably under sterile conditions in the operating room. If the hematoma has gone unrecognized too long and has progressed to the point of causing laryngeal compression and airway obstruction, then the skin and deep fascial sutures should be removed post haste at the bedside to release the hematoma. This should restore an adequate airway immediately, but if it does not, endotracheal intubation will be necessary. Bedside tracheostomy is warranted only as a last resort if laryngeal edema precludes intubation.

Postoperative airway obstruction may also occur secondary to *bilateral recurrent laryngeal nerve injury*. Initially, the cords usually will be flaccid and paralyzed in an intermediate position; the airway may or may not be adequate. Bilateral cord paralysis should always be suspected in patients in whom stridor and cyanosis develop shortly after extubation. Immediate reintubation must be carried out, but one does not need to do an emergency tracheostomy. The problem may be simply one of neuropraxia or even simple laryngeal edema, both of which are reversible. We have had experience with several such patients who, after one or two days of endotracheal intubation and parenteral steroid therapy, could be safely extubated without subsequent airway problems. Of course, if the cords are paralyzed and the airway is compromised, tracheostomy will be necessary ultimately. If there is no return of cord function during the subsequent 6 to 12 months, transoral arytenoidectomy is performed to enlarge the airway by laterofixation of one cord. Attempts at delayed nerve repair[26] or nerve muscle pedicle implants as described by Tucker[32] have generally not been successful in restoring cord function. In those patients in whom the airway is initially adequate despite bilateral cord paralysis, the voice is hoarse and breathy at first; later its quality improves. This may mean that nerve function has recovered, but it may also have a more ominous significance signaling impending airway compromise. This is because when the cords remain paralyzed, the glottic aperture becomes progressively more narrow as atrophy, fibrosis, and contraction in the intrinsic laryngeal muscles draw the cords into a tense midline position. Permanent bilateral recurrent nerve paralysis is perhaps the most serious complication of thyroid surgery. Fortunately, it is a rare occurrence: Colcock and King[8] reported only one case in more than 30,000 thyroid operations.

Injury to the external branch of the superior laryngeal nerve is frequently discussed, and much is made of the vulnerability of this branch when the superior vascular pedicle of the thyroid is clamped (Fig. 1, no. 1). But there is no simple way to document such injury, and therefore its true frequency is quite unknown. Voice changes that occur are usually of an extremely subtle nature and will probably go unnoticed by the patient unless he or she is a professional singer or public speaker. The patient may be aware of an inability to reach high-pitched sounds (the superior laryngeal nerve innervates the cricothyroid muscle, which is a tensor of the vocal cord), or easy fatigability of the voice when speaking to crowds. Injury to this nerve can best be avoided by leaving division of the superior pole vessels until after the isthmus has been divided and the lobe has been

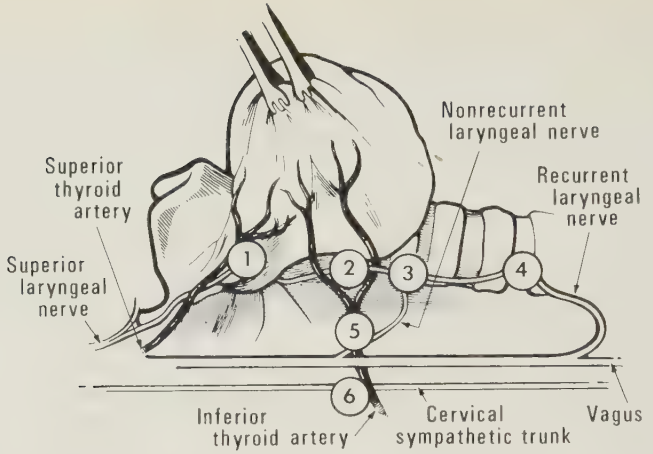

Figure 1. Sites of possible nerve injury in thyroidectomy (see text for discussion). (*From* Edis, A. J., Ayala, L. A., and Egdahl, R. H.: Manual of Endocrine Surgery. New York, Springer-Verlag, 1975, with permission.)

substantially mobilized. The adventitial tissue attaching the upper pole of the thyroid to the larynx is then divided. This leaves the lobe suspended by the superior vascular pedicle. Now the thyroid lobe can be swung away from the larynx in order to suture-ligate and divide the superior thyroid vessels while the superior laryngeal nerve is left medially and protected from injury.

Other rare neurologic complications of thyroid and parathyroid surgery include injury to the cervical sympathetic trunk (it is vulnerable when the inferior thyroid artery is ligated), causing Horner's syndrome (Fig. 1, no. 6); damage to the phrenic nerve, in the course of a modified neck dissection for metastatic thyroid carcinoma, causing paralysis of the hemidiaphragm; and transection of the spinal accessory nerve during nodal dissection of the posterior triangle, causing drooping of the shoulder and winging of the scapula from paralysis of the trapezius muscle.

The right lymphatic duct or thoracic duct may also be injured in the course of a modified neck dissection. Leakage of chyle will usually be obvious during operation, at which time it is an easy matter to ligate the duct. Attempted repair of this friable, thin-walled vessel is inadvisable, because a persistent leak will almost certainly result, with the subsequent development of a chylous fistula. Reoperation will then be required to ligate the duct in the neck or, if this fails, in the chest.

MORE FREQUENT COMPLICATIONS

Unilateral Paralysis of the Recurrent Laryngeal Nerve

Indirect laryngoscopy should be performed as a routine, both preoperatively and postoperatively. In these times of heightened medicolegal sensibility, it is important to document normal vocal cord function before operation, even if there is no previous history of neck surgery. In such cases, cord paralysis may be related to the thyroid disease

itself or to unsuspected intrathoracic pathology such as tracheal neoplasm or aortic aneurysm. Occasionally, one will also encounter so-called idiopathic vocal cord paralysis in which there is no apparent cause.[21] In patients who have had previous operations on the thyroid or parathyroid gland, it is doubly important to know of the presence of cord paralysis before reoperation, not only because of the potential medicolegal implications but also because of the concern about possibly injuring the remaining functional nerve and causing airway obstruction.

If the surgeon takes pains to identify the recurrent nerves at operation and refrains from handling them directly with instruments,[16] iatrogenic injury causing permanent paralysis rarely occurs. *Transient cord paresis* is not uncommon, even in the best of hands, and is presumably due to edema of the nerve, but it seldom, if ever, lasts more than four to six weeks. The surgeon should be aware that trauma from the endotracheal tube itself can cause temporary cord paralysis.[20] Apparently the cuff of the tube can directly compress peripheral branches of the recurrent nerves[14] and cause injury. Even bilateral vocal cord paralysis can occur as a direct result of endotracheal intubation.[15]

If the nerve is severed in the course of dissection and the injury is recognized at the time, one should attempt to reapproximate the cut ends immediately with the use of meticulous microsurgical technique and 7–0 suture material. Unfortunately, there is not much hope that full recovery will occur.[29] Delayed nerve repair is essentially worthless.[26] The recurrent laryngeal nerve is most vulnerable to injury in the course of thyroid lobectomy when the inferior thyroid artery is being tied off (Fig. 1, nos. 2 to 4) and when the ligament of Berry is divided (this is a dense condensation of connective tissue that binds the thyroid posteriorly to the first and second tracheal rings). In rare instances (0.3 per cent)[30] the nerve may be nonrecurrent on the right side, and it is then particularly vulnerable when the artery is being tied off (Fig. 1, no. 5). After primary subtotal or total thyroidectomy, the incidence of permanent unilateral recurrent nerve paralysis is less than 1 per cent (0.5 per cent of nerves exposed to risk) in good hands. Of course, the risk increases sharply with secondary surgical procedures, approximating 10 per cent.[3]

Unless routine indirect laryngoscopy is performed, many instances of cord damage will never be discovered. This is because compensatory overadduction of the uninvolved cord narrows the glottic chink to produce a normal voice. When symptoms occur, they are usually those of hoarseness and an ineffective nonexplosive type of cough, but even in these patients, a normal-speaking voice will almost always return in time as fibrotic changes in the paralyzed muscles move the cord from a paramedian position to the midline. If after 6 to 12 months there has not been spontaneous recovery of nerve function, the quality of voice can often be improved by the injection of Teflon paste into the paralyzed cord.[1]

Complications Related to Overtreatment or Undertreatment

Patients are often referred after a *subtotal thyroid lobectomy for carcinoma* when frozen-section diagnosis was either not available or was not sought at the time of operation because the lesion was thought to be

grossly benign. Several days later, to the surgeon's consternation, a diagnosis of thyroid carcinoma is returned after examination of the permanent sections. The patient now faces a second procedure, with all its attendant risks. Clearly, it is inappropriate to subject a patient to operation for the express purpose of ruling out malignancy in a thyroid nodule and not obtain a pathologic frozen section. The operation should be tailored to suit the specific lesions encountered.

Thus, papillary or follicular carcinoma is best resected by total lobectomy on the side of the tumor and near-total resection of the contralateral lobe.[10] One-half to 1 gram of thyroid tissue is left on the contralateral side to safeguard the recurrent laryngeal nerve on this side and to preserve at least one parathyroid gland intact, unless there is multicentric or bilateral disease—in which case a total thyroidectomy is performed. Medullary carcinoma, especially of the familial variety, should be treated by total thyroidectomy. En bloc modified neck dissection, preserving the cosmetically important sternocleidomastoid muscle, is performed if metastatic thyroid cancer is evident in cervical nodes either clinically or at the time of operation. The recent work of Mazzaferri et al.[18] highlights the importance of postoperative thyroid hormone therapy and radioiodine ablation of any residual tissue exhibiting iodine uptake in cases of papillary and follicular cancer. This therapy is a vital corollary to surgical care and should not be neglected by the surgeon.

Lifelong thyroid hormone suppression therapy is also recommended after partial thyroidectomy for benign adenomatous disease. Although there is still considerable argument as to whether thyroxine treatment can bring about regression of established benign nodules, there is general agreement that such treatment will tend to prevent recurrence of adenomatous goiter after subtotal thyroidectomy.

Inadequate thyroid resection in Graves' disease (especially in children) will lead to recurrence and usually the necessity for radioiodine treatment—a form of therapy one had hoped to avoid by surgery in the first place. When performing a subtotal thyroidectomy for Graves' disease, we leave about 1 to 2 grams of tissue on either side. Perhaps by so doing we incur a somewhat higher incidence of *postoperative myxedema,* but the size of the thyroid remnant is only one of several factors that determine thyroid status after surgical treatment of thyrotoxicosis. Others include the degree of lymphocytic infiltration of the gland, the presence of complement-fixing thyroid antibody in the serum, the length of follow-up, and the natural progression of thyrotoxicosis to spontaneous hypothyroidism. Best estimates are that the surgeon should expect a cumulative incidence of postoperative hypothyroidism of about 25 to 30 per cent within the first 10 years after operation, with a recurrence rate of less than 5 per cent. There is obviously a clinical and ethical responsibility for lifelong supervision of these patients. Some authors have suggested administering thyroid hormone to all patients after thyroidectomy for Graves' disease, recognizing that many will eventually require it in any case. This is unsound practice because many of these patients will have persistently nonsuppressible thyroid function, and routine thyroid hormone administration may lead to iatrogenic thyrotoxicosis.

Perzik[25] has recently advocated *total thyroidectomy for Graves' dis-*

ease as well as for a variety of other benign thyroid conditions. The fact that he is able to perform this operation with low morbidity is a tribute to his surgical skill but does not justify his advocacy of this radical surgical approach. Perzik's claim that total thyroidectomy prevents the development of exophthalmos is not supported by any controlled study.[9] Moreover, to propose total thyroidectomy for granulomatous thyroiditis, Hashimoto's disease, and adenomatous goiter flies in the face of accepted mores of treatment and exposes the patient to unnecessary morbidity and even potential mortality.

Cosmetically mutilating classic radical neck dissection for metastatic papillary carcinoma is another example of surgical overtreatment of thyroid disease. There is now ample evidence[2, 5, 18] that neither the risk of recurrence nor the ultimate survival rate is compromised if the surgeon spares the cosmetically important sternocleidomastoid muscle and spinal accessory nerve. Dissection of nodes in the submaxillary triangle is also seldom necessary, because these nodes are outside the primary or secondary zone of thyroid lymphatic drainage. Adequate exposure for a modified neck dissection is provided by a curved extension of the standard thyroidectomy "collar" incision upward along the posterior border of the sternocleidomastoid muscle. This avoids the disfiguring end result of the "H" incision commonly used for classic radical neck dissection. The indication for neck dissection in patients with papillary thyroid carcinoma is the presence of palpably enlarged or characteristically discolored (blue-black) metastatic lymph nodes in the lateral neck region. There is no place for "prophylactic" dissections searching for microscopic involvement in otherwise normal-appearing cervical nodes.

Postoperative hypocalcemia after thyroidectomy may be due to a number of different factors. According to Wilkin et al.,[36] thyrocalcitonin may play a role, and in patients with Graves' disease there may be absorption of calcium salts by hungry bones in repair of a chemical osteodystrophy.[19] However, the first practical consideration is that the parathyroids have been damaged. Parathyroid glands may be injured, devascularized, or inadvertently removed in the course of thyroidectomy, If the damage is severe enough, overt hypoparathyroidism will result, usually within one to seven days after operation. The patient complains of undue anxiety or apprehension or appears unusually depressed. Circumoral or acral paresthesia is an early symptom and when it is present the Chvostek sign is usually positive. Treatment should be initiated before Trousseau's sign becomes positive. This tends to occur late and is usually an indication of severe hypocalcemia with impending carpopedal spasm, laryngeal stridor, and convulsions.

Wade et al.[33] have pointed out that there may be lesser degrees of hypoparathyroidism after thyroidectomy without symptoms of paresthesias and agitation. These patients can remain chronically hypocalcemic for long periods, suffering vague ill-health and even the insidious development of cataracts or mental disorders. The serum calcium level should be monitored postoperatively on a daily basis until it has stabilized within the normal range. Hypocalcemia per se does not require treatment, but if there are accompanying symptoms or signs of heightened neuromuscular irritability, therapy is indicated.

Acute, severe symptoms with full-blown tetany and carpopedal spasm will require urgent intravenous administration of calcium (10 ml of 10 per cent calcium gluconate by *slow* intravenous injection over three to five minutes). Subsequent calcium needs over the next few hours can best be met by titrating an intravenous drip of 500 ml of normal saline containing 20 to 30 ml of 10 per cent calcium gluconate. Oral therapy can be started at the same time. Mild symptoms of hypocalcemia usually respond well to oral calcium supplements in the form of calcium carbonate or calcium lactate administered on a six-hourly basis. Calciferol or dihydrotachysterol may be added to enhance calcium absorption if oral calcium alone is not sufficient to maintain a normal serum level. It is usual to discontinue use of the vitamin D preparation after normocalcemia has been maintained for several weeks; ultimately, the oral calcium supplement can also be stopped. All patients who require treatment for postthyroidectomy hypocalcemia should have the parathyroid function reevaluated from time to time after all treatment has been discontinued, keeping in mind that they may have diminished parathyroid reserve.[33]

The incidence of permanent hypoparathyroidism after thyroidectomy—even after total thyroidectomy—should be less than 5 per cent. Thompson and associates[31] have demonstrated that a rate of 2 per cent can be achieved by painstaking dissection of the parathyroid glands in situ. More recently, Paloyan et al.[22] have reported a zero incidence of permanent hypoparathyroidism in a series of 54 consecutive total thyroidectomies. They attributed their results to routine autotransplantation of any parathyroid glands that had become devascularized in the course of dissection. Autotransplantation of otherwise nonviable glands is a good idea, but it is hoped that the Paloyan group's results will not be misinterpreted as justifying a more cavalier attitude toward the parathyroids simply because autotransplantation is available. It is obviously best to preserve the parathyroid glands intact with their own blood supply if at all possible.

A certain degree of hypocalcemia is not entirely unwelcome after parathyroidectomy for hyperparathyroidism because it gives some assurance of cure, but *hypocalcemia sufficient to cause symptoms* represents significant morbidity and should be avoided if at all possible. As is true after thyroidectomy, treatment is not indicated unless symptoms are present, but no patient should be dismissed home until the serum calcium level has returned to normal levels. Hypocalcemia after parathyroidectomy is caused by hypoparathyroidism (when the level of serum phosphorus is high) or "bone hunger," that is, the rapid accretion of calcium into demineralized bone (when the serum phosphorus level is low). Bone hunger is most likely to occur in the 5 per cent or so of patients with hyperparathyroidism who have preoperative radiologic evidence of osteitis. Some of these patients may also have deficits of magnesium which will require replacement postoperatively. Symptomatic hypoparathyroidism is much more common if one follows a policy of routine subtotal parathyroidectomy for primary hyperparathyroidism, as has been recently advocated,[23] than if one follows traditional surgical guidelines and selectively removes enlarged glands.[11] It stands to reason that the more parathyroid tissue removed, the greater is the likelihood for postoperative

hypoparathyroidism. Bruining[6] reported a 37 per cent incidence of permanent hypocalcemia after prophylactic subtotal parathyroidectomy as compared with only 1.2 per cent when only enlarged glands were removed, and a prospective study by Edis et al.[11] comparing the two operative strategies yielded very similar results. The original premises justifying routine subtotal parathyroidectomy[13, 23] have been shown to be invalid.[7, 28] This operation should be reserved for patients who have bona fide chief cell hyperplasia, for which, in our experience, it has proved to be a satisfactory treatment. We do not agree with Wells et al.[35] that these patients with primary chief cell hyperplasia should be treated by total parathyroidectomy and autotransplantation of parathyroid tissue into the forearm.

Persistent hyperparathyroidism results most often from the surgeon's overlooking a single parathyroid adenoma, which is frequently accessible to removal from the neck.[12, 34] Most cases of failed neck exploration result from the surgeon's lack of familiarity with the normal location of the parathyroid glands and the way in which the glands may be displaced during embryologic development or later during adult life. The surgeon must be prepared to explore from the angle of the jaw above into the superior mediastinum below.

The most common complication of reoperative parathyroid surgery is permanent hypoparathyroidism.[12, 34] It occurs usually because the normal parathyroid glands had been either destroyed or removed at the first operation (often in the mistaken belief that they are "hyperplastic"), and excision of the missing adenoma removes the last functioning gland. It is here that parathyroid autotransplantation has an important application. Grafting a portion of the tumor into the forearm musculature in these cases circumvents the permanent hypoparathyroidism that would otherwise inevitably occur. These grafts will eventually be capable of supporting a eucalcemic state after a variable period of support with oral calcium and vitamin D.[35] Parathyroid autotransplantation should be considered in all patients coming to reoperation if there is any concern that the normal glands have been removed. One can either transplant the tissue immediately, or a portion of the tumor can be cryopreserved if the facilities are available and transplantation can be performed if tetany supervenes. If recurrent graft-dependent hypocalcemia subsequently occurs, it is easily managed by resecting a portion of the implanted parathyroid tissue under local anesthesia.

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The APUD Cell System and Its Neoplasms

Observations on the Significance and Limitations of the Concept

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In the last decade, endocrine pathology has undergone a notable development. The application of electron microscopy, cytochemistry, and immunopathology as well as refinements in more established techniques and disciplines such as tissue culture, biochemistry, and histochemistry have produced vast amounts of information about the structure and function of normal and abnormal endocrine cells and tissues. But this evolution has not been merely technical; parallel to it, and partly at least facilitated by modern techniques, interesting conceptual advances have taken place. Among the latter, the development of the APUD cell system concept is of particular interest.

The idea that some endocrine cells populating the gastrointestinal tract and some viscera embryologically derived from it may be related to neural tissues is not entirely new.[31] Keen observers as P. Masson and F. Dänish noted similarities between neural cells and carcinoid tumors.[13, 42] Feyrter consistently advocated the existence of a complex endocrine system consisting of isolated cells distributed throughout the gastrointestinal tract and associated tissues and viscera which he termed "peripheral endocrine-paracrine glands."[17]

The common denominators that bridge these widely dispersed cells are cytochemical and structural. Early studies ascribed to these cells high amine precursor (5-hydroxytriptophan) uptake, high alpha-

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glycerophosphate dehydrogenase, and high esterase or cholesterase levels. Subsequent investigations clarified these cells' cytochemical properties and resulted in the introduction of the acronym APUD (*A*mine *P*recursor *U*ptake and *D*ecarboxylation) and the progressive evolution of the concept.[46] These cells appear to be capable of taking up materials such as DOPA or 5-HT, decarboxylating them, and subsequently producing biogenic amines. By using the latter as building units increasingly complex peptides may result.[46]

At the electron microscopic level, APUD cells tend to display a prominent rough endoplasmic reticulum and Golgi complex and abundant free ribosomes. The distinctive ultrastructural feature of the APUD cells is the presence of round secretory granules consisting of a single delimiting membrane, a pale halo, and a more or less central core of variable density and appearance. The size of these granules ranges from 50 to 400 nm or more, but falls mostly within the 100 to 250 nm range. Occasional structures of similar electron microscopic appearance may be found in non-APUD cells, and the appearance and distribution of the granules in APUD cells may vary considerably;[22] therefore, considerable care is required in their identification.[21]

We feel that it may still be premature to present a "definitive" list of APUD cells. Nevertheless, important attempts have been made and these have included the peptide secreting gastric and intestinal cells, all pancreatic islet cells, the cells of the adrenal medulla, and all extraadrenal paraganglia, the hypophyseal ACTH, MSH, FSH, LH, and TSH producing cells, the parafollicular thyroid cells, the melanoblasts, and so on.[46, 48] The controversy regarding the parathyroid chief cells appears to have been resolved in favor of their inclusion within the APUD system. Also, additional cells with APUD characteristics may be found in the gastrointestinal, respiratory, and urogenital tracts, although their possible secretory materials and their function remain speculative.[46, 48] Recently, the possible inclusion of the Merkel cell of the skin within the APUD system has been suggested.[34, 64]

The embryogenesis of the APUD system has evoked considerable interest. In experiments involving the study of animal embryos in sequential stages of development, migration of cells with APUD characteristics from the neural crest to an eventual destination in the primitive gut and derivatives appeared to have been established.[46] The passage of APUD cells through the mesoderm and the colonization of the intestine were monitored by means of radioautography or formalin induced fluorescence (FIF) and by the identification of grafted neural cells between closely related but nevertheless recognizably distinct species. It was, therefore, tempting to suspect that all APUD cells were of neuroectodermal origin; however, conflicting data have been reported in this regard[50] and the controversy is far from resolved.

PATHOBIOLOGY OF SECRETION

The initial phase of the secretory process of protein and related materials, hormones or otherwise, takes place in the rough endoplasmic reticulum from which materials are transferred to the Golgi complex. In the

latter structure, the secretory product is concentrated, and the sugar component, if any, is added. Also, if the secretory product is to develop into a secretory granule, the delimiting membrane of the granule is acquired in the Golgi complex.[16, 37] Secretory granules may remain in the cytoplasm for variable periods of time (secretion storage) or they may proceed to the secretory pole of the cell. Intracytoplasmic displacement of secretory granules is neither passive nor random. Cytoplasmic microtubules and microfilaments play a crucial role in the secretory process as evidenced by the alterations that occur in this process following injury to the microtubular-filamentar system.[37] As the granule reaches the cell's membrane, the granule's membrane fuses with that of the cell, and the secretory material is ejected without loss of membrane material by the cell. This phase of the secretory process is termed exocytosis or emiocytosis.[16, 37] Excessive increases in the cell's membrane appear to be avoided through a membrane recycling mechanism.[37]

The mechanism of secretion described above describes steps common to a variety of glands, both exocrine and endocrine, but are particularly pertinent to the latter. Nonetheless, variations do occur, as in the case of thyroid follicles in which secretion storage is in part at least extracellular.

Schematically, as it pertains to APUD cells and their neoplasms, we may consider the secretory process to consist of a sequence of phases: initial synthesis occurring in the rough endoplasmic reticulum and with messenger RNA and the indispensable nuclear carriers and enzymes; addition of sugar component, if any, condensation, and "maturation" that occur in the Golgi complex in which the granules acquire their delimiting membrane; intracytoplasmic transport via the microtubular-filamentar system; emiocytosis; and ? recycling of membrane material. This exceedingly complex mechanism provides numerous possible sites where defects may occur in neoplastic or otherwise abnormal cells. Since neoplasms are known to have chromosomal abnormalities which in turn may alter proper expression of gene function, aberrations in the secretory process of neoplastic cells are hardly surprising, and these secretory aberrations may be reflected in tumors that secrete and/or store "ectopic" or multiple hormones, may produce hormones but fail to release them, or may produce materials that are incapable of evoking a detectable target response.[22]

ULTRASTRUCTURAL, BIOCHEMICAL, AND CLINICAL CORRELATIONS

This discussion will be limited to some examples of neuroendocrine tumors. By this arbitrary restriction we hope to present a more meaningful and in-depth discussion of certain selected features that may be common to other neuroendocrine tumors.

Pancreatic Islets and Their Neoplasms

Conventional histochemistry was generally satisfactory in the differential staining of the various types of islet cells; however, when those stains were applied to islet cell neoplasms, the results were often disap-

pointing, and when correlations were attempted with the clinical hormonal activity of those tumors, discrepancies often arose. This apparent contradiction prompted electron microscopic studies that clearly demonstrated wide variabilities in the ultrastructural appearance of the secretory granules.[20] Thus pancreatic islet tumors associated with mild hypoglycemia may consist of cells displaying abundant and mature granules with characteristic paracrystalline profiles (Fig. 1). On the other hand, cases with extremely severe hypoglycemia may be related to neoplasms whose cells display a relative overconcentration of immature granules (Fig. 2). Moreover, one may incidentally encounter islet cell tumors in surgical or autopsy specimens, and these may display abundant mature granules, despite the absence of detectable hormonal or metabolic abnormality (Fig. 3).

This notable morphologic variability in the number and appearance of the secretory granules has also been reflected by immunoreactivity studies and has evoked several possible explanations.[21, 23] It seems most likely, however, that some islet cell neoplasms as well as other neuroendocrine tumors may comprise cells that produce substances which may or may not be identical to the secretory products of their non-neoplastic counterparts. Thus it was suggested that the "immature" granules seen in some islet cell neoplasms may reflect an arrested stage in the maturation process or perhaps an even more complex deviation of the normal secretory mechanism.[20-22]

It has been demonstrated that the A and B segments of insulin are formed as parts of one polypeptide chain in the form of a loop held by disulfide bonds; this precursor material has been termed "proinsulin."[57]

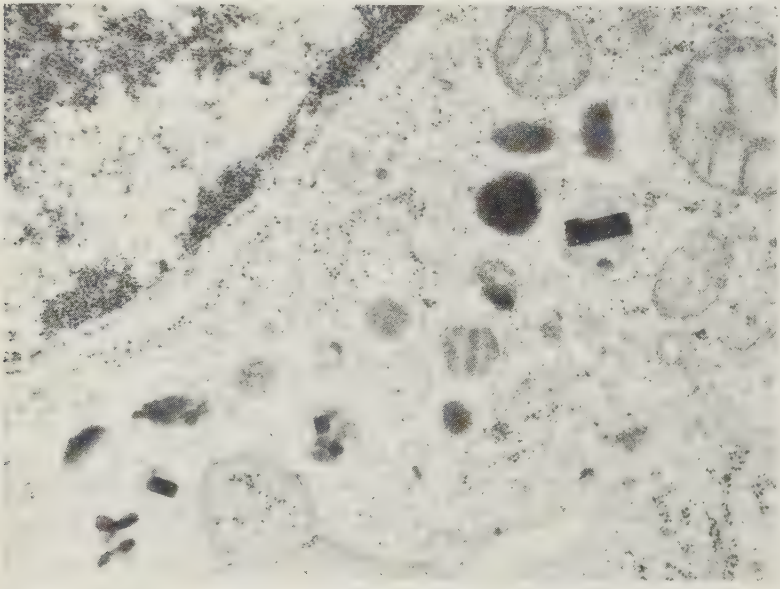

Figure 1. Islet cell adenoma in a 52 year old woman. Clinically, she had a history of several years of occasional episodes of mild hypoglycemia. Notice prominent secretory granules, some of which display paracrystalline profiles. (× 44,500.)

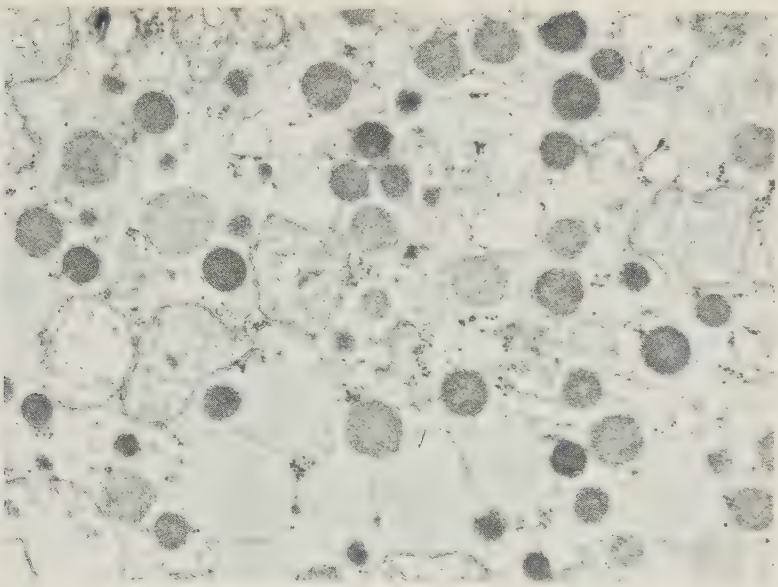

Figure 2. Islet cell carcinoma in a 40 year old man. Clinically, he had a history of extremely frequent episodes of profound hypoglycemia. Notice abundant secretory granules of variable density and absent paracrystalline profiles. (× 41,000.)

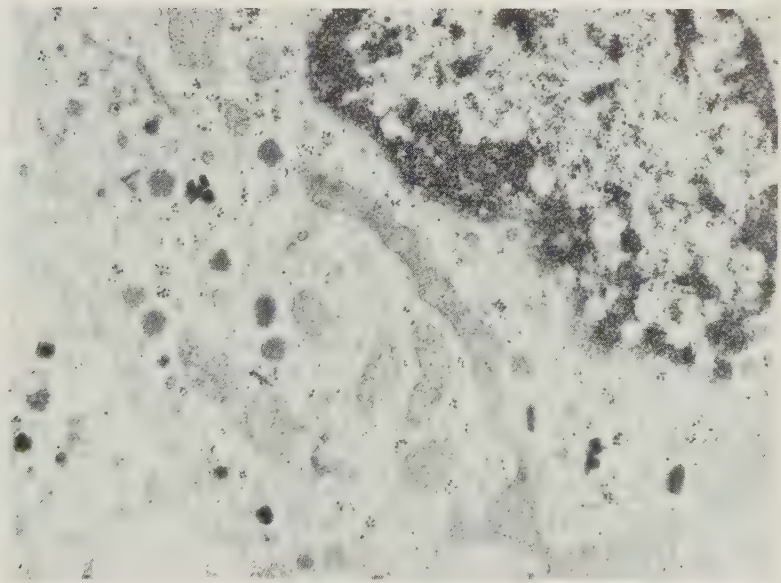

Figure 3. Islet cell adenoma was an incidental autopsy finding in a 69 year old woman who had a history of progressive cardiac failure. There was no history of hormonal or metabolic abnormalities. Notice secretory granules with and without paracrystalline profiles. (× 24,500.)

Subsequently, a protease removes a portion of the loop resulting in insulin which is represented ultrastructurally by the mature granules with the characteristic paracrystalline profiles. Interestingly, while proinsulin is indeed produced normally by non-neoplastic beta cells, their neoplastic counterparts produce it in relatively larger amounts. These observations would suggest that a given islet cell tumor may produce respectable amounts of proinsulin—or other prohormones—but a decreased or absent enzyme converting system necessary to activate the hormone could result in a clinically silent tumor. The reverse situation may also apply; that is, a neoplasm with minimal prohormone production but an active converting system may be heralded by a dramatic clinical syndrome. Other possibilities for derangement evidently exist such as defects in the microtubular-filamentar system resulting in lack of hormone release by the tumor cells despite abundant as well as mature secretory granules.

The development of the proinsulin concept has been extended to other hormones including progastrin,[26] proglucagon, proparathohormone,[27] pro ACTH,[18, 68] and so on. By inference, it appears likely that many neuroendocrine tumors regardless of primary site may secrete materials in their prohormonal or other abnormal forms; these secretory products may or may not be "ectopic" and may or may not result in clinical hormonal syndromes or detectable metabolic abnormalities. Recent experiments involving the transfer into Xenopus eggs of messenger RNA obtained from several hormone-producing neoplasms resulted in the secretion of a common protein precursor with a molecular weight of 65,000. These data suggest that in neoplastic endocrine cells precursors would be acted upon and the type of hormone(s) produced may be variously altered by modified enzyme systems associated with the endoplasmic reticulum.[41]

Adrenal Medulla and Its Neoplasms

In the non-neoplastic adrenal medulla, epinephrine and norepinephrine are secreted by a single cell type. These secretory products are closely related but are nevertheless structurally and biochemically different, and their pharmacologic effects are also distinct. Both materials are produced concomitantly but epinephrine is secreted more abundantly than is norepinephrine. At the ultrastructural level, this functional situation is demonstrated by the larger number of relatively smaller, dense cored granules characteristic of epinephine as compared with the fewer but larger norepinephine granules with their typically eccentric core.[21, 22]

Pheochromocytomas may exhibit variable electron microscopic appearances; both epinephrine and norepinephrine are secreted but the latter generally exceeds the former. This pattern of secretory activity holds true for both benign and malignant types of pheochromocytoma. Thus, we detect another variant of aberrant secretory activity in which tumor cells seemingly reverse the functional pattern of their non-neoplastic counterparts. Also characteristic of adrenal pheochromocytomas is that they almost invariably display a clinical hormonal syndrome; clinically "silent" pheochromocytomas appear to be distinctly rare.[60]

Neuroblastomas, ganglioneuroblastomas, and ganglioneuromas rep-

resent variants of cellular differentiation and clinical behavior of neoplasms derived from a presumably single cell type. That these tumors are capable of producing and storing variable amounts of biogenic amines has been shown by biochemical and electron microscopic studies.[32] This is clinically important since determination of vanillylmandelic acid (VMA) and related substances has become part of the standard armamentarium in the clinical differential diagnosis of these tumors.

However, while pheochromocytomas are almost invariably associated with a clinically evident hormonal syndrome, neuroblastomas and ganglioneuroblastomas seldom are "functional" in that sense. Thus we are confronted with yet another variant of aberrant secretory patterns displayed by a group of tumors which differs from those of other closely related neoplasms and also from the single cell type from which they all presumably arise.

Interesting and somewhat similar abnormalities in the secretory activity of neoplasms derived from the extraadrenal paraganglia have been discussed and illustrated.[22]

Gastrointestinal Chromaffin Cells and Their Neoplasms

Histogenetically, there is little doubt that the chromaffin cells populating the gastrointestinal tract constitute a single group. Functionally, they appear to be capable of producing a wide variety of amine and peptide materials whose roles remain incompletely understood. *Carcinoids* are the best known group of neoplasms that originate from those cells. By light microscopy, these tumors display rather consistent morphologic patterns that tend to overlap regardless of primary site. Noteworthy, however, is that while ileal carcinoids are often accompanied by a more or less characteristic "carcinoid syndrome," their counterparts in the stomach, appendix, and rectum seldom display a hormonal syndrome. The heterogeneity of this group of cells and consequently of the neoplasms arising from them was already suggested by the variable distribution of argentaffin versus argyrophil elements. Ultrastructurally, carcinoids invariably display rather abundant neurosecretory type granules but their size and electron density may vary within a broad range.[22]

Recently our attention has been focused on a rather small group of gastric and colonic carcinomas which by conventional light microscopy are generally classified "undifferentiated." These tumors are recognizable as epithelial cancers but lack glandular differentiation, and their reactivity to stains for mucosubstances is either extremely faint or altogether negative. Silver stains for granules may or may not be helpful. Occasionally, focal light microscopic appearances led to suggestions that some of these tumors may indeed represent "anaplastic" variants of carcinoids. These and similar observations by others stimulated us to apply a combination of ultrastructural and biochemical analysis to the study of these tumors.[9, 24] By electron microscopy, neurosecretory granules were demonstrated in several cases. The relative ease with which granules can be shown in material not originally processed for electron microscopy and even in deparaffinized tissues indicated again that they are indeed very

durable structures.[24, 33] Biochemically, the demonstration of appreciable concentrations of VMA, 5-hydroxyindolacetic acid (HIAA), and catecholamines in these tumors provided additional evidence of their endocrine origin or differentiation. These data, in turn, suggest not only the possible pathologic reclassification of these neoplasms but may lead the way to newer diagnostic and therapeutic approaches.[9, 24]

Tracheobronchial Kulchitsky Cells and Their Neoplasms

The existence of the Kulchitsky cells in the tracheobronchial tree and their close relationship to the enterochromaffin cells have been evident for some time. These cells display characteristic neurosecretory granules. Their product(s) of secretion and their possible function remain unclear,[7] but current data suggest that these cells are part of the APUD system.

"Oat" or small cell undifferentiated carcinomas constitute a group of bronchopulmonary neoplasms of rather typical morphology and clinical evolution. Until rather recently they were thought to belong within the broader group of "bronchogenic" carcinomas and consequently were presumed to be of endodermal derivation. However, a number of electron microscopic, biochemical, cytochemical, and tissue culture studies have strongly suggested that these neoplasms may derive from Kulchitsky cells and may indeed belong within the neuroendocrine or APUD system.[5, 25, 26, 28, 43, 47, 62] Given these observations and prompted by the light microscopic similarities between the aforementioned "undifferentiated" gastrointestinal carcinomas and these pulmonary neoplasms, we applied combined ultrastructural and biochemical methods to the study of the latter. Not surprisingly, we were able to demonstrate that some oat cell pulmonary carcinomas contained neurosecretory type granules, and biochemical analysis of tumor tissue samples revealed detectable concentrations of VMA, 5-HIAA and catecholamines.[25] Moreover, we obtained similar results when the study was extended to include some "larger" cell undifferentiated pulmonary carcinomas,[25] which suggested that the neuroendocrine group of bronchopulmonary neoplasms may include tumors other than the typical carcinoids or oat cell carcinomas.

MISCELLANEOUS APUD CELL HYPERPLASIAS, DYSPLASIAS, AND NEOPLASMS

Focal *hyperplasia* involving the C or parafollicular cells of the thyroid has been extensively investigated particularly in relatives from patients with medullary carcinoma. Ultrastructurally, these hyperplastic C-cell foci seemingly consist of two characteristic cell populations differing in the distribution of the cytoplasmic organelles including variations in the number and size of the neurosecretory granules.[15] These observations appear to parallel those made in medullary carcinoma and other neuroendocrine tumors which can and often do produce more than one hormone or prohormone.

Nesidioblastosis (see below) is also an example of APUD cell hyperplasia. These exuberant islet cells are clearly capable of producing

several hormone-type materials (see below); however, their characteristic clinical manifestation appears to be hypoglycemia.

Several years ago Gewirtz and Yalow demonstrated the presence of circulating pro-ACTH in dogs with experimentally produced bronchial epithelial *dysplasias*.[28] In a study of neuroendocrine cells in human dysplastic bronchial epithelium, significant abnormalities were found in the number, size, and distribution of the secretory granules as well as in the Golgi complex.[23] Since similar bronchial epithelial changes may be found in chronic non-neoplastic pulmonary disease, it would be tempting to speculate that some of the peculiar paraneoplastic syndromes occasionally associated with the latter might result from abnormal secretory activity by the former.[23]

Reports of possible APUD cell neoplasms of numerous primary sites which were associated with variable hormonal syndromes are indeed abundant.[56] Carcinomas arising within or around the thymus with characteristic neurosecretory granules and presenting with or without hormonal syndromes have been observed.[14, 22, 40, 53] More unusual examples include small cell "neuroendocrine" carcinoma of the uterine cervix associated with ACTH production and Cushing-like syndrome.[35] We have recently studied a similar case which by immunocytochemistry appeared to contain somatostatin as well as ACTH.[54] We have also studied a primary skin carcinoma of adnexal type; ultrastructurally the tumor contained abundant neurosecretory granules (Fig. 4), and elevated serum calcitonin levels were repeatedly demonstrated. A total thyroidectomy revealed no C-cell abnormalities and a follow-up period of over seven years revealed no other tumor or lesions which could be held responsible for the over-

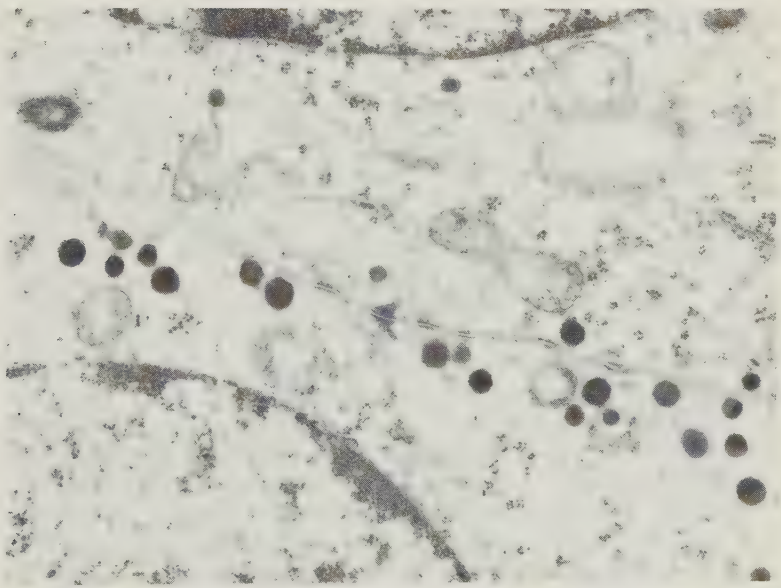

Figure 4. Skin carcinoma in a 77 year old woman with elevated levels of calcitonin. Prominent dense-cored secretory granules are evident. (× 26,400.)

production of calcitonin.[34] We have speculated that such skin carcinoma might have arisen from the so-called Merkel cell whose membership in the APUD system was recently proposed.[64]

Immunocytochemical Aspects

Various immunocytochemical techniques have been employed to visualize polypeptide hormones within cells. The first of these methods involves the use of fluorescein-labelled antibodies, a technique pioneered by A. H. Coons.[10] The technique localizes an antigen (in this case the hormone) by binding of the fluorescein-labelled antibody to it and visualization of the regions of fluorescence in the tissue section by means of a specialized microscopy system. The method is extremely sensitive and fairly standardized. However, it requires the use of fresh, usually frozen cryostat sections and specialized dark-field ultraviolet microscopy. The slides are not permanent and, therefore, photographic documentation is required.

The development of enzyme-linked antibodies[44] provided an alternate method for the localization of antigens, especially in routinely fixed paraffin embedded tissue sections. The most widespread technique of this type employs horseradish peroxidase as the enzyme source. A recent review described thoroughly these techniques from a practical and theoretical standpoint.[61] The direct immunoperoxidase technique employs a peroxidase-labelled primary antibody with specificity for the antigen being visualized. Although it is the simplest of the immunoperoxidase techniques, it usually requires an abundant source of purified monospecific labelled antibody that may or may not be commercially available. Often, it is less sensitive than the other available immunohistologic techniques. The indirect immunoperoxidase technique is more complicated but its advantages are that peroxidase labelled antibodies to a variety of animal immunoglobulins are commercially available, it is more sensitive, and it usually requires lower concentrations of antigen specific first antisera for visualization of the antigen. The third method developed by Sternberger[58] employs peroxidase-antiperoxidase complex in an antibody bridge technique. In this case the first antibody which is antigen specific is raised in a particular animal species, for example, rabbit. The second antibody is a divalent IgG antibody raised against antibodies of the first species, for example, goat-anti-rabbit IgG. The second antibody acts as a bridge and binds the third antibody which in turn has been raised in the same animal species as the first antibody and is directed against horseradish peroxidase as the antigen. In performing this procedure, the first and second antibodies are overlaid in sequence and the peroxidase-antiperoxidase complex is added as a third step. Although a somewhat cumbersome technique, this method is extremely sensitive and may be 100 to 1000 times more sensitive than immunofluorescent techniques.

The major advantages of the immunoperoxidase methods are that they can be utilized on routine formalin-fixed paraffin embedded sections in which morphology is well preserved. They result in permanent section that can be studied using routine light microscopic equipment. The same immunoperoxidase reagent may also be used to visualize antigens in electron microscopic ultrastructural correlations.

Utilizing a variety of these techniques a number of neuroendocrine tumors and other lesions have been studied. The best documented cases of hormone production in neuroendocrine related tumors are medullary carcinomas of the thyroid gland which derive from the "C" (or parafollicular) cell of the thyroid.[8, 29] The parafollicular cell or C cell in the human thyroid has been identified both ultrastructurally and cytochemically as a cell with neuroendocrine features deriving from the neural crest. In addition the presence of the hormone calcitonin has been identified in C cells in human thyroid gland utilizing both direct and indirect immunoperoxidase techniques.[66, 67] In these elegant studies of both adult and neonatal human thyroid glands, the distribution of C cells as identified by positive immunoperoxidase staining for calcitonin was correlated with the calcitonin content of the thyroid gland. Utilizing the same technique they also demonstrated that in patients with C cell hyperplasia belonging to a group of familial multiple endocrine adenomatosis (MEA syndrome), the multifocal distribution of hyperplastic C cells correlated with the distribution of C cells in normal thyroid glands.[65] The chief areas of hyperplasia corresponded to the areas of highest C cell concentration in the upper two-thirds of the lateral lobes of the thyroid gland. In addition, they demonstrated positive immunoperoxidase staining for calcitonin in medullary thyroid carcinoma. In a more extensive study of medullary thyroid carcinomas, Capella et al.[8] demonstrated a heterogeneity of hormone-producing cells in a series of medullary thyroid carcinomas. In addition to positive immunoperoxidase staining for calcitonin, the presence of immunoreactive ACTH and somatostatin-containing cells was identified by immunoperoxidase staining specific for these hormones. One of their patients had Cushing's syndrome and the greatest numbers of ACTH producing cells were found in this patient's tumor. Apparently different populations of cells were responsible for each different hormone identified.

Morphologic heterogeneity is a fairly consistent feature of neuroendocrine neoplasms arising in other sites. This observation is strikingly apparent in neuroendocrine neoplasms of the gastrointestinal and respiratory tracts.[9, 24, 25] Although the embryogenesis of the endocrine cells of the pancreas itself remains somewhat controversial, ultrastructurally and biochemically they have characteristic features found in other neuroendocrine cells. The tumors that they produce have a broad spectrum of hormones, some of which are associated with distinctive clinical syndromes, for example, hypoglycemia and Zollinger-Ellison syndrome. Immunoreactive insulin,[2] glucagon,[38] gastrin,[12] somatostatin,[36] and vasoactive intestinal polypeptide (VIP)[6] have all been demonstrated in islet cell tumors. In addition, tumors with multiple hormones including ACTH and human pancreatic polypeptide have been described in islet cell tumors as well as in carcinoid tumors of the small bowel.[1, 12, 39, 51] In these cases when one or more hormones were present, the clinical syndrome, when present, was usually a manifestation of one of the hormones being secreted. This heterogeneity of hormones in these tumors reflects the staggering heterogeneity of hormones found in neuroendocrine cells scattered throughout the gastrointestinal tract. Interestingly, many of these hormones have been localized in both the brain

and gastrointestinal tract as has been pointed out by Pearse in a recent overview of the APUD concept.[49]

The immunoperoxidase technique may also provide useful information when applied to non-neoplastic neuroendocrine lesions. A diffuse proliferation of islet cells occurs in infants and is associated with persistent hypoglycemia with inappropriately elevated insulin levels; it has been termed nesidioblastosis.[20] Utilizing both direct and indirect immunoperoxidase procedures, a patient with nesidioblastosis was studied from a quantitative morphologic viewpoint.[4] In addition to overall increases in insulin, glucagon, somatostatin, and pancreatic polypeptide hormone producing cells, there was a diffuse scattering of these cells throughout the exocrine portion of the pancreas. A section of this pancreas, which has been stained for both insulin and somatostatin utilizing a double staining immunoperoxidase technique[45] for multiple tissue antigens, is demonstrated in Figure 5. The staining of both insulin and somatostatin is well shown. Quantitative morphologic analysis was used to determine the relationship of insulin to somatostatin cells in both islet and nonislet locations. In this case, the vast majority of insulin cells (<90

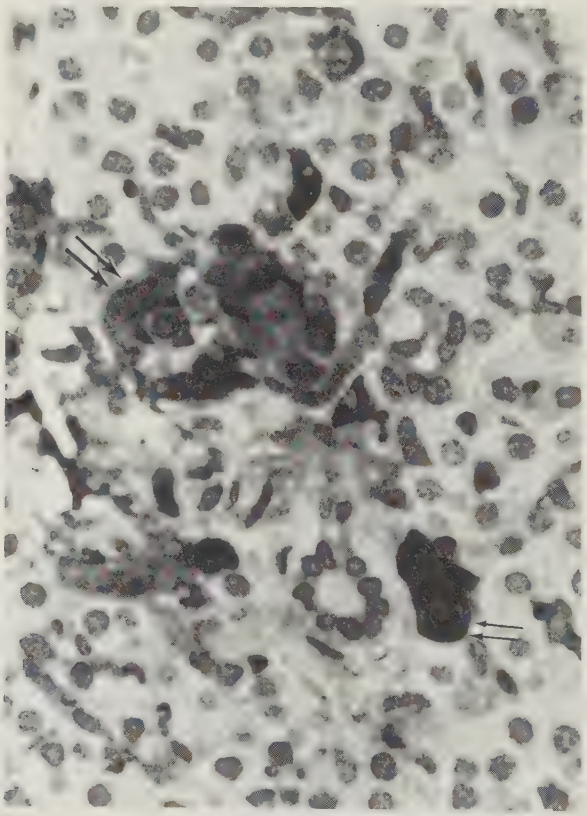

Figure 5. Nesidioblastosis in an eight month old female infant. Immunoperoxidase stain for insulin and somatostatin. Small clusters of insulin-containing cells (thin arrows) and somatostatin-containing cells (thick arrows) are seen around the ductules in the exocrine portion of the pancreas. Exocrine cells remain negative for both stains. (× 450.)

per cent) occurred adjacent to one or more somatostatin cells, suggesting that at least at the light microscopic level the normal interrelationship between insulin and somatostatin cells usually seen in islets is retained even in the extra islet derangement seen in this patient with nesidioblastosis. We also confirmed the observations of Heitz et al.[30] whereby a significant underestimation of the magnitude of the islet cell proliferation would have been made if only routine histology methods had been employed. These observations may be important in future studies of sudden infant death which may be related to nesidioblastosis,[11, 52] and of nesidioblastosis associated with multiple endocrine neoplasia syndromes.[63]

The most common hormones associated with oat cell carcinomas are ACTH and ADH.[3] However, immunoreactive ACTH has been found in all histologic subtypes of lung carcinoma, predominantly in the prohormone form of big ACTH.[28] The overwhelming majority of lung cancers associated with Cushing's syndrome are oat cell carcinomas and, when studied, these patients tend to secrete corticotropin releasing factors in addition to ACTH.[59, 69] The demonstration of immunoreactive ACTH by immunoperoxidase in oat cell carcinomas has been variable,[55] and may reflect loss of immunoreactivity by the molecule secondary to tissue processing. In addition to ACTH, oat cell carcinomas have been associated with the production of calcitonin, antidiuretic hormone, insulin, vasoactive intestinal polypeptide, and gastrin, again reflecting the heterogeneity of hormone production by these tumors.[70]

SUMMARY AND CONCLUSIONS

The development of the APUD cell system concept has provided us with a fascinating hypothesis and stimulated much needed research in endocrine pathology. Some puzzling phenomena pertaining to production of "ectopic" hormone by some neoplasms and the various syndromes of multiple endocrine neoplasms may be explained by the APUD concept.

If we consider the proposed theory of common histogenesis of these neoplasms, then ACTH secretion by an oat cell pulmonary carcinoma ceases to be truly ectopic and becomes merely a slightly deviated functional expression of neoplastic neuroendocrine cells. Also, we may consider that multiple hormone production, synchronous or asynchronous, may simply reflect the fact that many of these neoplastic cells possess and express variable biosynthetic capabilities within a single basic framework. It also becomes apparent that those neuroendocrine neoplasms that become manifest by clinically evident hormonal syndromes are perhaps only the tip of the iceberg. We believe that there are many neoplasms currently classified as undifferentiated which may also belong within this family as suggested by biochemical and ultrastructural studies. These tumors may produce either "prohormones" or other materials that do not result in clinical hormonal syndromes. Yet these materials or their metabolites may be detected and quantitated, and this observation may have future diagnostic as well as therapeutic implications.

A few sobering remarks appear also in order regarding possible limitations of the APUD concept: recent experimental work suggested that perhaps some APUD cells may not be of neuroectodermal derivation; the membership list of the APUD cell system will very possibly undergo revisions as our knowledge increases; and certain paraneoplastic syndromes and certain hormonal syndromes associated with various neoplasms (for example, the hypoglycemia related to some sarcomas) may not be explainable within the APUD concept.

We feel that careful clinical observation when combined with data derived from various research techniques will eventuate in a more accurate classification of some endocrine neoplasms, and may subsequently result in their improved diagnosis and treatment.

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Multiple Endocrine Neoplasia Type IIb

The Most Aggressive Form of Medullary Thyroid Carcinoma

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Only recently have the combined clinical anomalies of multiple endocrine neoplasia type IIb (MEN IIb) and their common neuroectodermal origin been fully recognized. Five case reports serve to emphasize the almost pathognomonic physical appearance of patients with this disease. The characteristic facies with multiple mucosal neuromas, the marfanoid habitus, and the disturbances in bowel function may be present from an early age. These stigmata should alert the clinician to the possibility of MEN IIb before its more lethal components, medullary thyroid carcinoma and pheochromocytoma, are clinically manifest.

All five patients described herein had palpable neck masses when first examined and, at initial surgery, tumor spread beyond the thyroid gland was evident, in four of the five patients. Widespread metastatic medullary thyroid carcinoma has since developed and two patients have died as a result of the disease. Although medullary thyroid carcinoma pursues a relatively indolent course in subjects with the syndrome MEN IIa, in patients with MEN IIb it is expressed in its most virulent form.

It has been 20 years since Hazard, Hawk and Crile[9] described the unique neoplasm medullary thyroid carcinoma. This tumor is characterized histologically by the presence of an amyloid staining stroma and parafollicular or "C-cells" which are derived from the neural crest. Calcitonin, a hormone secreted by the C-cells, serves as a plasma tumor marker and often is elevated in patients with medullary thyroid carcinoma even though the tumor is not evident clinically. Intravenously administered calcium ion[14, 15] and pentagastrin[10, 18, 19] are potent secretagogues which are especially useful in the early diagnosis of either primary or recurrent medullary thyroid carcinoma.

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Whereas medullary thyroid carcinoma usually occurs sporadically, it may be present as a component part of two complex endocrine syndromes. Multiple endocrine neoplasia type IIa (MEN IIa) is a disease inherited as an autosomal dominant trait and is characterized by the concurrence of medullary thyroid carcinoma, pheochromocytoma(s), and parathyroid hyperplasia. A similar malady, which may either arise sporadically or occur in a familial pattern, is multiple endocrine neoplasia type IIb (MEN IIb).[5] This disease has also been termed multiple endocrine neoplasia type III[13] or the mucosal neuroma syndrome.[16] Williams and Pollock[21] were the first to describe the clinical entity in which multiple mucosal neuromas, pheochromocytoma, and medullary thyroid carcinoma were combined. A small number of case reports suggestive of this syndrome were found in the literature prior to Williams' article; however, the authors apparently failed to recognize the complete range of abnormalities present. The typical physical appearance of patients with MEN IIb was first described in detail by Gorlin and associates[6] and Schimke et al.[17] The patients have a characteristic facies with soft tissue prognathism, "blubbery" or "bumpy" lips, broad base of the nose, everted eyelids, and multiple mucosal neuromas. These plexiform neuromas consist of an unencapsulated tangled mass of nerves and scant connective tissue. Medullated corneal nerve fibers are apparent on slit-lamp examination. Patients commonly have a "marfanoid habitus" and are slender with poor development of body musculature. Skeletal abnormalities such as dorsal kyphosis, pectus excavatum, pes cavus, and a high arched palate may be present. Scoliosis, lordosis, and valgus deformities of the knees or toes have been recorded. Gastrointestinal complaints are common in patients with MEN IIb and often antedate palpable disease in the neck. Typically constipation occurs early in life; however, in older patients diarrhea is more common. Bartlett[1] and Schimke[17] have suggested that the ganglioneuromatosis commonly seen in these patients may cause defective peristalsis and poor contractility which result in constipation. The mechanism producing the diarrhea is unknown, but may be hormonal. Studies by Gray and associates[8] have implicated high plasma levels of calcitonin as one possible etiologic agent.

CASE REPORTS

A distinct clinical feature not stressed sufficiently in previous reports has been the biological aggressiveness of medullary thyroid carcinoma in patients with MEN IIb. The five case reports illustrate the usual clinical findings in patients with this disease.

Case 1

This four year old male presented with tender, enlarged cervical and supraclavicular lymph nodes on the right. Biopsy of a cervical node revealed poorly differentiated carcinoma with invasion of muscle. The patient was referred to Duke University Medical Center for further management.

The past medical history was noncontributory except for a three year history of diarrhea. The family history was negative for thyroid or adrenal tumors. Two older siblings were of normal habitus, and without neck masses or bowel symptoms.

On physical examination, the patient was a thin, white male of marfanoid habitus. He was 111 cm in height (75th percentile) and weighed 15.5 kg (10th percentile). He had a prognathic jaw, prominent lips (Fig. 1A), and gingival hypertrophy. Neuromata were evident on the tongue and medullated corneal nerve fibers were easily visible on slit-lamp examination. A 3 by 2 cm hard mass was present in the right thyroid lobe, and firm, fixed right cervical and supraclavicular nodes were evident. The serum calcium and phosphorus concentrations were normal as were 24 hour urinary levels of vanillylmandelic acid, epinephrine, and norepinephrine. The basal level of plasma calcitonin was 134,000 pg per ml (normal <200 pg per ml). A chest x-ray film revealed a soft tissue neck mass compressing the trachea.

A neck exploration was performed. Local tumor spread was extensive, involving the sternocleidomastoid muscle and encircling the trachea and right carotid artery. The tumor was not resectable; however, a biopsy confirmed the diagnosis of medullary thyroid carcinoma. A permanent tracheostomy was placed for relief of upper airway obstruction, and the patient subsequently received 5000 rads of X-irradiation to the neck. He has done poorly since that time with no significant weight gain. His larynx and trachea are now completely fixed, and there has been recurrent difficulty in securing an adequate airway.

Figure 1. Four patients with multiple endocrine neoplasia type IIb: *A*, Case 1; *B*, Case 2; *C*, Case 3; *D*. Case 5.

Case 2

At 12 years of age, this white male was first seen at the referring hospital for bilateral neck masses that had been noted six months earlier. He underwent a total thyroidectomy and bilateral radical neck dissection. Medullary thyroid carcinoma was present in both thyroid lobes and in 1 of 32 resected cervical lymph nodes. At the age of 13 years, he was referred to the Duke University Medical Center for evaluation of recurrent disease.

The patient reportedly suffered trauma at birth and developmental landmarks were delayed. At six months of age, severe constipation was noted; however, this resolved and by age two years, he began having watery diarrhea. The diarrhea disappeared after the thyroid surgery. The family history was negative for the presence of thyroid or adrenal abnormalities.

On physical examination, he was 159 cm tall (75th percentile) and weighed 38.5 kg (25th percentile). He had the characteristic facies of MEN IIb (Fig. 1*B*), including large bumpy lips, widespread teeth, and a prominent jaw. Multiple papillary lesions covered his anterior tongue (Fig. 2). He had a marfanoid habitus with long, thin extremities, pectus excavatum, and bilateral pes cavus. Hyperlordosis and thoracolumbar scoliosis were present. Bilateral talipes equinovarus deformities were noted. Slit-lamp examination of the cornea revealed hypertrophic corneal nerve fibers.

The serum concentrations of calcium and phosphorus were normal. Twenty-four hour urine values for vanillylmandelic acid, epinephrine, and norepinephrine were normal. The basal level of plasma calcitonin was 2600 pg per ml. The peak plasma level of calcitonin two minutes after the intravenous administration of pentagastrin (0.5 μg per kg over 5 sec) was 88,000 pg per ml. A chest x-ray film and radionuclide scans of the bones and liver were normal. Over the next year, the basal level of plasma calcitonin rose to 17,000 pg per ml, and the frequency of diarrhea increased. The patient's tumor was unresponsive to intravenous chemotherapy consisting of doxorubicin hydrochloride (360 mg total dose) and 5-fluorouracil (1000 mg total dose) and subsequently streptozotocin (9 gm total dose). His current plasma calcitonin level is 30,000 pg per ml, and chest x-ray films and liver scans demonstrate findings consistent with metastatic medullary thyroid carcinoma.

Case 3

This eight year old black female presented with a three and one-half year history of an enlarging right neck mass. A left subtotal thyroid lobectomy and a right total thyroid lobectomy with radical neck dissection were performed at the referring hospital nine months before she was evaluated at the Duke University Medical Center. Medullary thyroid carcinoma was evident histologically in both thyroid lobes and in 7 of 53 resected lymph nodes. Postoperatively, she received X-irradiation in a dose of 5000 rads to the neck.

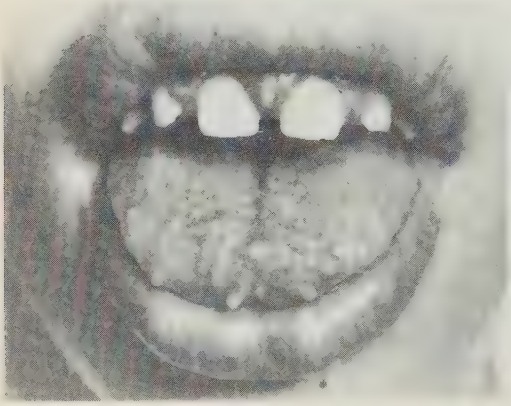

Figure 2. Multiple mucosal neuromas on the tongue in Case 2.

She had chronic constipation and at her previous hospitalization was found to have sickle cell trait. Although she was active and kept up with her peers, she had always been small for her age. There was no family history of thyroid or adrenal tumors and her four siblings were normal in habitus without stigmata of MEN IIb.

Physical examination revealed that the patient was below the 5th percentile in both height and weight. She appeared marfanoid in habitus and had long, thin extremities, pes cavus, and slight dorsal kyphosis. She had large bumpy lips (Fig. 1C), gingival hypertrophy, and multiple neuromata over her tongue, lips, and eyelids. Prominent corneal nerves were detected on ophthalmologic examination.

Serum concentrations of calcium and phosphorus were normal. Twenty-four hour urine levels of vanillylmandelic acid, epinephrine, and norepinephrine were also normal. Her basal level of plasma calcitonin was 800 pg per ml, and following provocative stimulation with pentagastrin the plasma calcitonin level at two minutes was 25,000 pg per ml. A chest x-ray film, intravenous pyelogram, and liver scan were all unremarkable.

Currently she is being followed with biannual provocative testing with calcium gluconate and pentagastrin. Her current peak plasma calcitonin level following provocation is 32,000 pg per ml.

Case 4

The diagnosis of MEN IIb was not made in this 31 year old white man until an autopsy was performed. At age 15 years, a left thyroid mass was discovered. The patient had a left thyroid lobectomy and a left radical neck dissection. "Adenocarcinoma of the thyroid" was detected in the resected thyroid lobe, and in multiple lymph nodes of the neck dissection specimen.

At the time of his initial surgery, several polypoid lesions were removed from the pharynx. No histologic report of these lesions could be located. He was known to have similar lesions on the tongue and lips. He did well until the age of 22 years when he again presented with an enlarging neck mass. A right thyroid lobectomy was performed, and histologic examination revealed "poorly differentiated adenocarcinoma" with nodal metastases. Postoperatively he received a course of cobalt therapy to the neck and superior mediastinum.

The family history was negative for endocrine tumors.

At the age of 31 years, the patient died, the terminal event being one of bronchopneumonia and progressive respiratory failure. At autopsy, the body was cachectic. Multiple mucosal neuromas were present over the tongue and lips, and intestinal ganglioneuromatosis was evident. Medullary thyroid carcinoma metastatic to the lungs, hilar nodes, pleura, and liver was found. Review of the slides from his two previous operations confirmed the diagnosis of medullary thyroid carcinoma. Multiple pheochromocytomas were found in both adrenal glands. Histologic sections from a tumor mass in the head of the pancreas revealed a probable primary islet cell tumor.

Case 5

This 28 year old white female (Fig. 1D) was referred for the management of widely metastatic medullary thyroid carcinoma. At the age of 26 years, she first noticed a neck mass. One year later, she underwent partial thyroidectomy and a right radical neck dissection. Medullary thyroid carcinoma was present in both thyroid lobes and seven of seven resected cervical lymph nodes contained tumor. Postoperatively, she received a total of 4500 rads to the neck and another 3000 rads to the superior mediastinum. Over the next six months, a progressively enlarging mediastinal mass and pulmonary nodules were noted on chest x-ray films. Filling defects were noted in the liver on radionuclide scanning.

As a child, she had been chronically constipated and required an enema for weekly bowel movement. She stated that she had always been thin and weak compared with her siblings. At the age of 26 years, she developed diarrhea which ceased following thyroid surgery. It recurred, however, as the extent of metastatic disease increased. At the age of 26 years, she also began having episodes of tachycardia, pallor, diaphoresis, and nervousness. The remainder of the past medi-

cal history was unremarkable. She denied a family history of thyroid or adrenal tumors, and 10 siblings appeared to be normal, having none of the stigmata of MEN IIb.

On physical examination, the patient was tall and thin, with a marfanoid habitus. Her pulse was 120 per minute and her blood pressure was 100/70. She had multiple mucosal neuromas over the lips, tongue, and eyelids. Dorsal scoliosis and bilateral pes cavus deformities were evident. Ophthalmologic examination revealed thickened corneal nerves. A 2 by 2 cm right submandibular node and a 4 by 3 cm left axillary node were noted. The liver was not palpable.

The serum concentrations of calcium and phosphorus were normal. A twenty-four hour urine collection revealed an epinephrine of 47 μg and a norepinephrine of 118 μg; the vanillylmandelic acid was 17 mg. The basal calcitonin level was 12,000 pg per ml, and rose 10-fold following pentagastrin stimulation.

With the appropriate preoperative preparation, the patient underwent laparotomy, and both adrenal glands were noted to contain pheochromocytomas. The lesion in the right adrenal was 8 by 6 cm, and was resected. The lesion in the left adrenal gland measured 1 by 1 cm. A liver biopsy confirmed the presence of metastatic medullary thyroid carcinoma. Numerous diverticula were noted in the large bowel.

The patient's disease continued to progress. A metastatic lesion in the vertebral column resulted in spastic paraparesis when the patient was 31 years of age. The basal plasma calcitonin level was 91,000 pg per ml at that time. The patient's final admission at age 31 years was prompted by the onset of a left facial paralysis. The terminal course was one of progressive respiratory failure owing to bronchopneumonia.

Autopsy study revealed metastatic medullary thyroid carcinoma to the lung, liver, ovary, and mediastinum. The superior mediastinal mass had completely eroded the wall of the trachea. The petrous portion of the left temporal bone was destroyed by a large necrotic tumor mass. This accounted for her recent neurologic deficit. Tumor also involved the seventh thoracic vertebra at the site of previous laminectomy. Extensive intestinal ganglioneuromastosis was evident.

DISCUSSION

The findings in our five patients with multiple endocrine neoplasia type IIb are summarized in Table 1. MEN IIb apparently developed sporadically in each patient, as careful questioning and examination of their siblings and parents failed to disclose evidence of familial disease. This is somewhat at variance with previously published reviews[4, 13] in which approximately 50 per cent of cases have been familial. Two of our patients were male and three were female; all but one were white. Each patient had the characteristic facies, marfanoid habitus, medullated corneal nerves, mucosal neuromas, and gastrointestinal symptoms previously described. Bilateral pheochromocytomas developed in the two oldest patients (Cases 4 and 5); however, the lesions were not discovered in one patient until autopsy. The reported incidence of pheochromocytomas in patients with MEN IIb is 56 per cent.[13] These lesions appear to develop relatively late. In those cases reviewed by Khairi,[13] pheochromocytomas were identified in only 23 per cent of patients under 20 years of age, but in 90 per cent of those over 20. The lesions are usually bilateral, but rarely extraadrenal. Patients with MEN IIb may have minimal signs or symptoms suggesting pheochromocytoma, and the diagnosis is occasionally made at autopsy after the patient succumbs to a hypertensive crisis. Patients with MEN IIa or MEN IIb must be carefully

Table 1. *Findings in Five Patients with Multiple Endocrine Neoplasia Type IIb*

	CASE 1	CASE 2	CASE 3	CASE 4	CASE 5
Family history	–	–	–	–	–
Sex	M	M	F	M	F
Race	W	W	B	W	W
Characteristic facies	+	+	+	+	+
Marfanoid habitus	+	+	+	+	+
Medullated corneal nerves	+	+	+	Unknown	+
Mucosal neuromas	+	+	+	+	+
Gastrointestinal disturbances	Diarrhea	Constipation then diarrhea	Constipation	Unknown	Constipation then diarrhea
Pheochromocytoma	–	–	–	+	+
Hyperparathyroidism	–	–	–	–	–
Age at diagnosis of medullary thyroid carcinoma (yrs)	4	12	4	15	28
Nodes at surgery	+	+	+	+	+
Metastatic medullary thyroid carcinoma	+	+	Unknown	+	+

evaluated to rule out the presence of a pheochromocytoma prior to performing thyroidectomy for medullary thyroid carcinoma.

None of our patients had hyperparathyroidism, and this has been the usual reported experience; however, two patients with MEN IIb and hyperparathyroidism have been described. Bartlett[1] reported a patient with documented MEN IIb who had an elevated serum calcium concentration (12.7 mg per dl). Medullary thyroid carcinoma and an associated parathyroid adenoma were resected at surgery. Block[3] reported a patient with MEN IIb who had borderline elevated serum calcium concentrations of 10.3 and 10.4 mg per dl. At surgery, the resected parathyroid tissue appeared hyperplastic microscopically, but the dimensions of the glands were not described.

The unusual physiognomy characterized by multiple mucosal neuromas, puffy lips, myotonia, and skeletal anomalies may be apparent at birth in subjects with MEN IIb. It is unknown, however, whether medullary thyroid carcinoma is also present at such an early age. Disease has been detected as early as four years by Bartlett and associates[1] who performed a prophylactic thyroidectomy in a child with the characteristic phenotypic appearance, but no physical signs of a thyroid tumor. Bilateral medullary thyroid carcinoma was evident and tumor had already metastasized to the regional neck nodes. In Cases 1 and 2 of the present series, medullary thyroid carcinoma was clinically evident at age four years, and regional node metastases were present at surgery. A total thyroidectomy and neck dissection were performed in Case 2; however, in Case 1, the tumor was unresectable because of carotid artery and tracheal invasion. Prior to the advent of a sensitive radioimmunoassay for measuring plasma calcitonin levels, the diagnosis of medullary thyroid carcinoma was suggested by the detection of a mass in the neck. Currently, it is often

possible to detect medullary thyroid carcinoma in a preclinical stage by documenting elevated plasma calcitonin levels either basally or following provocative testing.

Khairi and associates[13] reported a woman with well documented MEN IIb whose children, 14 and eight years of age, had the facies, mucosal neuromas, and marfanoid habitus typical of the syndrome. Although no thyroid abnormality was palpable in either child, occult medullary thyroid carcinoma was diagnosed in both; the 14 year old daughter because of an elevated basal plasma calcitonin, and the eight year old son because of an elevated plasma calcitonin level following infusion of calcium. Carney and associates[4] detected medullary thyroid carcinoma in a two year old child, apparently by provocative testing. In patients with MEN IIb, it appears likely that MTC is present at birth or soon thereafter. When MEN IIb kindreds are discovered, every effort should be made to evaluate all offspring at risk, whether or not they have the characteristic phenotype. It would seem reasonable to perform a total thyroidectomy in children with the typical physical appearance regardless of age since the likelihood of their developing medullary thyroid carcinoma, if they have not already, is virtually 100 per cent.

In a recent review of the literature,[13] the mean age of diagnosis of medullary thyroid carcinoma in patients with MEN IIb was 19.6 years compared with a mean age of 53 years reported for patients with sporadic medullary thyroid carcinoma.[12] In the present study, all five patients had bilateral medullary thyroid carcinoma (mean age at clinical diagnosis 12.6 years) which had metastasized to regional nodes by the time of initial neck surgery. By comparison, a recent study of patients with MEN IIa demonstrated that the mean age of diagnosis in 50 subjects with clinically evident medullary thyroid carcinoma was 34.3 years, and the youngest child detected was 14 years of age.[20] In 32 patients without clinically apparent medullary thyroid carcinoma who were diagnosed by provocative testing with calcium and pentagastrin, the mean age at diagnosis was 20.5 years, and the youngest child detected was seven years old. Eleven (33 per cent) of the 32 patients were under 15 years of age, and 11 (33 per cent) had no gross disease but either microscopic medullary thyroid carcinoma or C-cell hyperplasia in their resected thyroid glands. In the present study, all five patients had macroscopic medullary thyroid carcinoma at initial thyroid surgery. We could find no reports of only C-cell hyperplasia or microscopic medullary thyroid carcinoma in patients with MEN IIb.

A sensitive index of "curative" thyroidectomy in patients with medullary thyroid carcinoma is the postoperative level of plasma calcitonin following provocative testing. Accordingly, thyroid resection was "curative" in 85 per cent (22 of 26) of MEN IIa patients whose preoperative diagnosis was by provocative testing alone.[20] There are few similar studies evaluating patients with MEN IIb, although the incidence of "curative" surgery appears to be low. Carney and associates[4] in evaluating 15 patients with MEN IIb reported only two children, eight and five years of age, who were apparently free of disease clinically following thyroidectomy. Basal calcitonin levels in these children were <50 pg per ml; how-

ever, no provocative testing was reported. Block[3] reported a 29 year old man with MEN IIb who at thyroidectomy was found to have medullary thyroid carcinoma but no regional node metastases. Postoperative calcitonin levels were <50 pg per ml following calcium infusion (15 mg per kg over 4 hrs). Similarly, Bartley[2] reported a 39 year old woman with MEN IIb who after thyroidectomy had undetectable (<50 pg per ml) plasma calcitonin levels following calcium stimulation.

Approximately 40 per cent of patients with MEN IIb are reported to have died from their disease. Whereas most deaths have been caused by metastatic medullary thyroid carcinoma, some have resulted from pheochromocytomas. There have been few reported long-term evaluations of patients with MEN IIb, and the mortality in all probability is greater than 40 per cent. Indeed, of our five patients with MEN IIb, two have already succumbed to medullary thyroid carcinoma, death is imminent in a third, and metastatic medullary thyroid carcinoma is progressing rapidly in a fourth. By contrast, an evaluation of 103 patients from our study of seven kindreds with MEN IIa has revealed that only eight (8 per cent) have died from medullary thyroid carcinoma.

Surgical resection of the medullary thyroid carcinoma and pheochromocytomas represents the primary mode of therapy for patients with MEN IIb. Medullary thyroid carcinoma is relatively resistant to ionizing radiation and is not sensitive to ^{131}I therapy. Although Gottlieb and associates[7] reported that doxorubicin hydrochloride was effective in patients with metastatic medullary thyroid carcinoma, such has not been our experience or that of others.[11] We have also found cis platinum (three patients treated) and streptozotocin (three patients treated) ineffective for inducing remissions in patients with metastatic medullary thyroid carcinoma.

Although there is a great similarity between the clinical syndromes MEN IIa and MEN IIb, medullary thyroid carcinoma in patients with the latter disease develops at a younger age, metastasizes earlier, and is associated with a higher mortality. Medullary thyroid carcinoma occurring in patients with MEN IIb progresses relentlessly and rarely is cured by surgical or medical intervention.

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Recent Advances in the Diagnosis and Treatment of Insulinomas

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The diagnosis and subsequent therapy of insulinomas are often straightforward; however, in some cases, serious difficulties are still encountered. As early as 1935 Whipple and Frantz recognized these problems.[13] They reviewed the literature until that time and found that only 60 per cent of patients who were explored because of hypoglycemia were indeed found to have an insulinoma. They set up criteria to aid in the diagnosis of an insulinoma which have come to be called "Whipple's triad": the patient's symptoms occur with fasting or exercise; at the time of symptoms, the serum glucose is 50 mg per dl or less; and the symptoms are relieved by the administration of glucose. While these criteria were timely, they have proved to be rather nonspecific and may be found in other conditions that result in fasting hypoglycemia.

The ability to measure plasma insulin concentration by radioimmunoassay has greatly aided the current day physician in the diagnosis of insulin-secreting tumors of the pancreas. Today the diagnosis is made primarily by the demonstration of inappropriately elevated concentrations of circulating insulin levels especially at the time of hypoglycemia, i.e., a diminished glucose to insulin ratio. Still the differentiation of insulinomas from other hypoglycemic states may be difficult at times and time-consuming. A workup for insulinoma often includes a prolonged fast (up to 72 hours in some patients) and provocative testing with some or all of the following agents: glucagon, leucine, arginine, and tolbutamide. Despite these tests, there are still a number of patients in whom the blood sugar and insulin values are of borderline significance. The purpose of this paper is to review some recent advances which appear to have significantly improved the accuracy of diagnosis, the localization of tumors, and the ultimate therapy of patients with insulinomas.

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DIAGNOSIS

Measurement of Insulin, Proinsulin, and C-peptide

A great deal of recent information has been gathered concerning the secretion of insulin from the beta cells of the pancreatic islets in normal and abnormal states.[8] Within the beta cells, proinsulin is formed from the rough endoplasmic reticulum (Fig. 1). Proteolytic conversion of proinsulin results in a splitting of the proinsulin molecule into insulin and a connecting peptide (called the C-peptide). The C-peptide has been demonstrated to contain 31 amino acids and to be a major part of the connection between the A and B chains of insulin within the proinsulin molecule. After cleavage, C-peptide and insulin are stored in the beta cell granules and are subsequently liberated together during exocytosis.

Both insulin and C-peptide are released in equimolar concentrations from the beta cells. In addition, some proinsulin is also secreted into the circulation presumably from the secretory granules. Serum proinsulin and C-peptide concentrations can now be determined by sensitive and accurate techniques.[8, 9]

Proinsulin

The measurement of circulating proinsulin has proved to be very helpful in the diagnosis of insulin-secreting tumors of the pancreas. As demonstrated in Figure 2, patients with insulinomas have elevated serum proinsulin concentrations almost without exception.[9] Furthermore, the percentage of circulating total immunoreactive insulin which is composed of proinsulin is also increased in most instances. It has furthermore been suggested that malignant tumors can be differentiated from benign islet-cell lesions by measuring the percentage of proinsulin in the total insulin immunoreactivity. Carcinomas tend to have the highest percentage values of proinsulin, whereas a lower value uniformly signals a benign tumor. Recently a patient with low serum insulin concentrations during hypoglycemia was diagnosed as having an insulinoma solely on the basis that 66 per cent of the total circulating immunoreactive insulin levels were accounted for by proinsulin.[1] At operation an insulinoma was found.

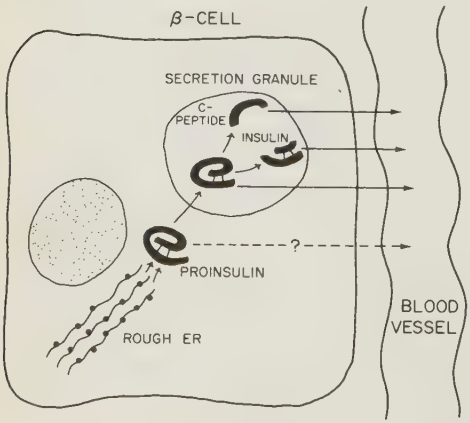

Figure 1. Conversion of proinsulin to insulin and C-peptide within the pancreatic beta cell. Equimolar amounts of insulin and C-peptide are liberated during exocytosis. ER signifies endoplasmic reticulum. (*From* Rubenstein, A. R., Kuzuya, H., and Horwitz, D. L.: Clinical significance of circulating C-peptide in diabetes mellitus and hypoglycemic disorders. Arch. Intern. Med., *137*:625, 1977, with permission.)

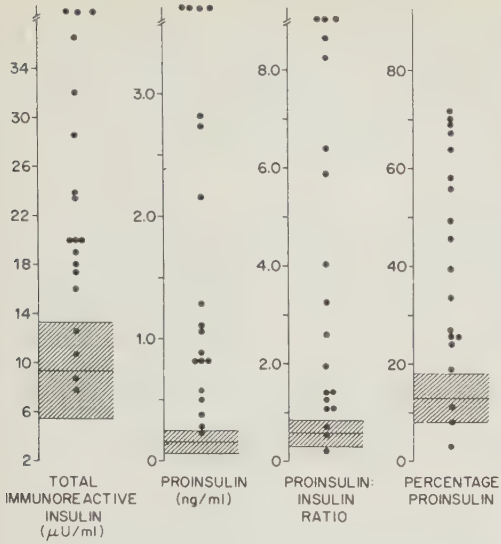

Figure 2. Basal total immunoreactive insulin (IRI), proinsulin-like components, proinsulin:insulin ratio, and percentage of proinsulin in 19 patients with insulin-secreting tumors of the pancreas. The mean ± 1 S.D. of 46 control subjects is shown in the hatched area. (*From* Rubenstein, A. R., Mako, M. E., Starr, J. I., et al.: Circulating proinsulin in patients with islet cell tumors. *In* Malaisse, W. J., and Pirart, J. (eds.): Diabetes. Proceedings of the Eighth Congress of the International Diabetes Foundation. Amsterdam, Excerpta Medica, 1973, pp. 736–752, with permission.)

C-peptide

The determination of serum C-peptide concentrations has also greatly aided the diagnosis of insulinoma in some patients and has also been helpful in ruling out other causes of hypoglycemia.[8] As described above, secretion from the beta cells results in an equimolar concentration of circulating C-peptide and insulin. Thus, changes in circulating C-peptide concentrations reflect beta cell secretion as do changes in serum insulin levels. Measurement of C-peptide concentration is especially useful in the following situations:

Diagnosis of islet cell tumors by the C-peptide suppression test. During this test, commercial insulin is infused into patients to induce hypoglycemia. As expected, with values of serum glucose of 40 mg per 100 ml or less, normal individuals suppress their endogenous secretion of insulin (as measured by serum C-peptide) by 50 to 70 per cent. In 11 of 12 individuals with surgically proven insulinomas, this suppression was abnormal, thus demonstrating a degree of autonomy in most tumors.

Diagnosis of islet cell adenomas (or beta cell hyperplasia) in diabetic patients who require insulin. Many patients who have taken or are currently taking insulin have circulating antibodies to this peptide which make measurement of serum insulin very difficult. This problem can now be circumvented by the use of the C-peptide assay, since this determination is not affected by insulin antibodies. An elevated C-peptide concentration in such cases is a reflection of increased endogenous secretion as would be expected in patients harboring an insulinoma.

Diagnosis of surreptitious injection of insulin. Another difficult problem has been the identification of patients who are secretly injecting themselves with insulin. Previously if elevated levels of serum insulin were found, one could not determine whether these results were caused by

the administration of commercial insulin or by endogenous insulin secretion. Now, this situation can be easily resolved by measuring both serum insulin and C-peptide levels at the time of hypoglycemia. A high circulating insulin concentration but low C-peptide value is indicative of administration of exogenous insulin, since commercial insulins contain no C-peptide.

Infusion of Calcium: A New Provocative Test for Insulinomas

Infusion of calcium has been utilized successfully as a provocative method for the release of gastrin, calcitonin, and serotonin and has thus aided in the diagnosis of gastrinomas, medullary carcinomas of the thyroid gland, and some carcinoid tumors.[6] Several years ago we demonstrated that infusion of calcium would also provide evidence for the presence of an insulin-secreting tumor.[4] In Figure 3, the results of infusion of calcium in four of our recently studied patients with surgically proven insulinomas are illustrated. Preoperatively, infusion of calcium resulted in a rise in serum insulin and a fall in concentrations of circulating glucose in each patient studied. The glucose to insulin ratio decreased to 1.5 or less in each patient within one hour of the start of infusion. Postoperatively, after successful resection of the tumors, infusion of calcium no longer produced changes in serum glucose or insulin. Thus far, infusion of calcium has resulted in no significant changes in levels of circulating glucose or insulin in normal individuals and in others with reactive hypoglycemia. We have become increasingly impressed by the results of this test for diagnosis of insulin-secreting tumors of the pancreas. Infusion of calcium appears to be rapid as well as safe.

PREOPERATIVE LOCALIZATION OF INSULINOMAS

Since most insulin-secreting tumors of the pancreas are only several centimeters or less in size, pancreatic ultrasound and computerized axial tomography (CAT scanning) have only limited usefulness. Similarly, endoscopic retrograde cholangiopancreatography (ERCP) is rarely helpful since these tumors are not ductal in origin. The two most impressive tests for preoperative localization are angiography and selective pancreatic vein catheterization with blood sampling.

Angiography

Angiography is undoubtedly the best of the commonly used tests for preoperative localization of insulinomas.[3] Many endocrine tumors of the pancreas are known to be vascular and thus to present as a blush on angiography. In the past, from 25 to 80 per cent of insulinomas were visualized by this method. Recent improvements in the technique of arteriography of the pancreas (highly selective injections, magnification, and subtraction procedures) have made these studies even more accurate. Subtraction techniques have proved to be the most important advance in this field. This procedure permits the elimination of confusing shadows that otherwise might be mistaken for tumors. A recent study from the Mayo Clinic utilizing these advanced methods demonstrated satisfactory tumor localization preoperatively in 30 of 34 (90 per cent) of

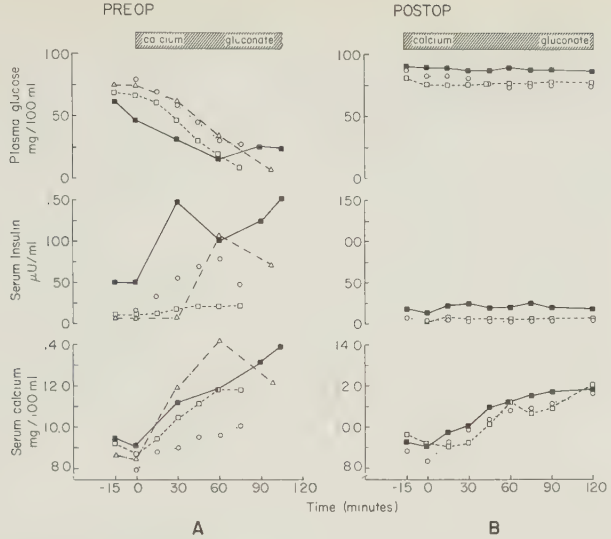

Figure 3. The changes of plasma glucose, serum immunoreactive insulin, and serum calcium concentrations which occurred during infusion of calcium gluconate, 5 mg of CA^{++} per kg per hour, into four patients with insulinomas. *A, Preoperatively.* An elevation of serum calcium levels was accompanied by a significant decrease in glucose concentrations and a rise in circulating insulin levels in each patient within two hours. *B, Postoperatively.* After successful tumor resection, a comparable rise in serum calcium concentration resulted in *no* changes in either serum glucose or insulin levels in three of these patients.

all cases of insulinomas that were studied.[3] We have been equally enthusiastic about the value of this technique. The preoperative localization by angiography of an insulinoma located in the head of the pancreas of one of our patients is illustrated in Figure 4. This tumor was later resected at operation.

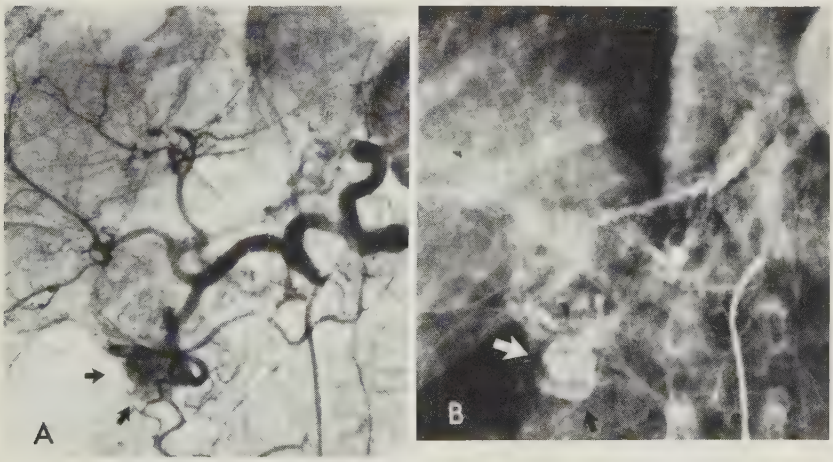

Figure 4. Preoperative localization of an insulinoma of the head of the pancreas by celiac artery angiography. *A,* Subtraction during the arterial phase. The tumor *(arrows)* is clearly seen. *B,* Venous phase. The tumor *(arrows)* is also well visualized. (Courtesy of Dr. Chien-tai Lu.)

Selective Pancreatic Vein Catheterization with Hormone Assay

Recently a technique has been developed in which the portal vein is catheterized transhepatically through a long needle.[7] The catheter is then guided into as many of the small pancreatic veins as possible. Blood is sampled from each area. The location of each specimen is carefully marked graphically. Hormone determinations are then performed on the serum samples. In suspected insulinoma, serum immunoreactive insulin is measured from each site. The location of an area of elevated serum insulin levels has correlated well with either the presence of an insulinoma or with a localized area of islet cell hyperplasia in five patients. This method has also been used successfully to diagnose and to localize the site of other islet tumors which were demonstrated to be glucagonomas, gastrinomas, or even a somatostatinoma because of the peptides that were secreted. We have only limited experience with this method; however, it appears to be very promising.

Value of Preoperative Localization Studies

In the recent Mayo study, 7 of 34 insulinomas could not be easily seen or palpated by the surgeon at the time of pancreatic exploration.[3] Our experience is similar. Since these tumors are often very small, we feel that successful preoperative localization greatly aids the surgeon. It reduces the time of operation, diminishes the need for "blind resection" of the pancreas, and probably improves the success rate of operation as well.

PATHOLOGIC CHARACTERISTICS

If operations are to be successfully performed, the surgeon must fully appreciate the pathologic characteristics of insulin-secreting tumors of the pancreas. Stefanini and associates summarized these in 1974 in an excellent review of the literature (Table 1).[12] They demonstrated that insulin-secreting tumors are located in almost equal number throughout the head, body, and tail of the pancreas. Those of the uncinate process (3 per cent) are especially difficult to find at operation unless a careful dissection is performed. About 1 per cent or less of all insulinomas are ectopic in location, but these are found close to the pancreas in most instances. Some may be located within the duodenal submucosa.

Insulinomas tend to be small tumors in most instances. About 40 per cent are 1 cm or less in size. In the Mayo series, 65 per cent of benign insulinomas were 1.5 cm or less in diameter.[2] Thus, the surgeon must be prepared to look for a small lesion. Few insulin-secreting tumors are 5 cm or greater.

Most insulinomas are single (87 to 92 per cent). When multiple (8 to 13 per cent), as many as eight different insulinomas have been found in a single pancreas. About half of the multiple cases have four or more insulinomas. When multiple insulinomas are found in the pancreas, the multiple endocrine adenomatoses, type 1 syndrome (MEA-1), should be especially suspected. In one of our recent patients, for example, four insulinomas were resected from the pancreas. Several years later she

Table 1. *B Islet Cell Tumors: Pathological Findings in 951 Completely Documented Cases**

	NO. OF CASES	%
Topography		
Head	305	32
Body	285	30
Tail	323	34
Uncinate	29	3
Ectopic	9	1
Size		
<0.5 cm	47	5
0.5–1.0 cm	323	34
1.0–5.0 cm	504	53
>5.0 cm	77	8
Number		
Single	789	83
Multiple	123	13
MEA	39	4
Parathyroid	16	1.5
Pituitary	10	1.0
Adrenal cortex	10	1.0
Thyroid	3	0.5
Nature		
Benign	798	84
Malignant	153	16
metastases	47	5

**From* Stefanini, P., Carboni, M., and Patrassi, N.: Surgical treatment and prognosis of insulinoma. Clin. Gastroenterol., 3:697, 1974, with permission.

developed hypercalcemia. At that time primary chief cell hyperplasia of the parathyroid glands was discovered and a subtotal parathyroidectomy was performed with a successful result. MEA-1 occurred in 4 per cent of the collected series of insulinomas. Parathyroid disease was the most commonly found associated lesion. Abnormalities of pituitary, adrenal cortical, and thyroid glands were also part of this syndrome.

Finally, in the collected series, 84 per cent of insulin-secreting tumors were found to be benign and 16 per cent were malignant. Only 5 per cent of tumors demonstrated frank metastases. In the Mayo series, 11 per cent of insulinomas were classified as malignant. In the latter studies, malignant lesions were defined as those having proven nodal or hepatic metastases, or demonstrating perineural or obvious vascular invasion. It has been pointed out that cellular pleomorphism, increased mitotic activity, and lack of encapsulation are unreliable indicators of malignancy in these lesions.

MANAGEMENT OF SERUM GLUCOSE CONCENTRATION

Preoperative Preparation

After an insulinoma is diagnosed, it is important that the patient be protected from the dangers of hypoglycemia until the operation is performed. This can be accomplished in most patients by frequent feedings.

On the evening prior to operation, an intravenous glucose solution should be started, since some of our patients have become symptomatic from hypoglycemia after only a two to four hour fast. In some institutions, diazoxide is begun preoperatively to alleviate the hypoglycemia. We prefer not to do so, however, since this impairs our ability to monitor changes in blood glucose values during operation.

Intraoperative Management

We have found the intraoperative monitoring of serum glucose concentrations to be helpful in many patients with an insulinoma. In the past, a glucose autoanalyzer was brought into the operating room and blood samples were obtained at 15 minute intervals for analysis. More recently we have used a continuous-flow, enzymatic system which determines and records the serum glucose values at one minute intervals.[10, 11] This machine is computerized so that one has the option of either maintaining the serum glucose concentration at a steady level by automatically infusing glucose or insulin as necessary, or one can permit the glucose values to change during operation and carefully observe the changes. Our initial impression of this "artificial beta cell," after studying the last three patients with insulinomas and more than a dozen other patients during operation by this method, is that this system is easily workable and that it may provide a greater degree of safety to the patient during operation.

In patients with insulinomas the major use of this monitoring system is to prevent hypoglycemia during operation. However, it may also aid the surgeon, at times, to determine when the tumor has been removed, since generally a rise in serum glucose values occurs within 30 to 60 minutes of this time. These data must be interpreted cautiously, however, since it has been clearly demonstrated that both false negative and false positive results may occur.[5]

Postoperative Management

After successful resection of an insulinoma, transient hyperglycemia is the rule. Generally the serum glucose values rise to the 200 to 300 mg per dl range for several days to two or three weeks. Thereafter, normal glucose metabolism is usually restored. Presumably this time is necessary for normal islet function to return. Some patients, however, particularly after subtotal or near-total pancreatectomy, may develop permanent hyperglycemia. Occasionally this complication occurs after a very limited resection or even after enucleation of an insulinoma. Diabetes mellitus is seen, of course, in all patients who require a total pancreatectomy. Postoperatively, we measure serum glucose values at least daily if they are abnormal. Insulin therapy is necessary if significant glycosuria or electrolyte disturbances occur. However, for transient hyperglycemia, no treatment is usually indicated.

OPERATIVE APPROACH

For most individuals, we favor a bilateral subcostal or an upper abdominal transverse incision. An upper midline incision should be per-

formed in those who have a narrow costal angle. It is important to examine the liver carefully for metastases and to obtain biopsy specimens of any enlarged lymph nodes along the portal triad. If preoperative angiography has localized a tumor, one should concentrate on this area initially; however, it is important to explore the entire pancreas even if a lesion is discovered, since multiple insulinomas occur in about 10 per cent of patients.

In order to examine the head of the pancreas, a Kocher maneuver should be performed by incising the peritoneum lateral to the duodenum. The duodenum and pancreas should be mobilized to the aorta. The body and tail of the pancreas can be examined by dividing the gastrocolic omentum inferior to the stomach and entering the lesser peritoneal space. The stomach is then elevated, some adhesions are divided, and the anterior surface of the body and tail of the pancreas is then visualized. The peritoneum inferior to the pancreas may then be incised and the body and tail of the pancreas can be mobilized. Often lesions can be seen on the anterior surface of the pancreas. They usually appear darker in color than the normal pancreas and may be reddish brown. Not uncommonly, however, a tumor that cannot be seen can be palpated as a harder area within the pancreatic substance. Abnormal lymph nodes in the area of an insulinoma should be biopsied and sent for frozen section diagnostic evaluation to rule out malignancy.

Most single or multiple lesions of the body or tail of the pancreas can be dealt with by a distal pancreatectomy although enucleation can be performed for small, single lesions on the surface of the pancreas. Lesions of the head are most frequently enucleated if there is no evidence of metastatic spread. One must be cognizant of the possible risk of injury to the common bile duct or to the major pancreatic duct in this area. A plane of dissection should be carefully developed immediately adjacent to the tumor and the lesion should then be gently removed. If one is concerned about the proximity of the common bile duct, this structure can be cannulated and later drained with a T-tube. Only rarely is it necessary or appropriate to perform a pancreaticoduodenectomy as the initial procedure for a small tumor of the head of the pancreas, for, in most instances, these are benign.

Malignant lesions of the pancreas should be treated as frank carcinomas. Distal pancreatectomy is appropriate for tumors of the body or tail of the pancreas, whereas a Whipple procedure or a total pancreatectomy should be performed for a malignant lesion of the head of the pancreas which is potentially curable. Even if cure is impossible, as much of the primary and metastatic disease should be resected as is safe, since often symptoms of hypoglycemia are palliated.

If an insulinoma cannot be found after performing these initial maneuvers, the spleen should be mobilized so that the tail of the pancreas can be more carefully examined. The uncinate process should be dissected and areas of possible peripancreatic ectopic lesions should be examined. A small duodenotomy should be performed and an attempt made to palpate submucosal or periduodenal nodules that may be present. Finally, if no insulinoma can be found, we favor the use of a "blind" distal resection of the pancreas. One should begin by progressively resecting the body

and tail of the pancreas up to the superior mesenteric vessels. The specimens should be carefully examined by the pathologist to determine whether or not an insulinoma is present. A rise in serum glucose values at this time is also reassuring to the surgeon although not a guarantee of cure. If no lesion is found, however, one should resect more pancreas; up to a 90 per cent distal pancreatectomy would seem appropriate. We do *not* favor the performance of a total pancreatectomy at this time, however, because sometimes a small tumor is later found in the specimen or a delayed rise in serum glucose concentrations might occur several hours after the resection.

Using such an operative technique, an occult insulinoma has been resected in 46 per cent to 85 to 90 per cent of patients in recently reported series.[2, 12] Furthermore, other patients with islet cell hyperplasia have benefited by this resection as well. Before performing a total pancreatectomy at a later date, we feel that a trial of diazoxide should be given to see if the hypoglycemia can be controlled by this drug. Only if this medical regimen fails should total pancreatectomy be considered.

RESULTS OF THERAPY

In the recent review of 1012 cases,[12] it was shown that 10 per cent of patients developed diabetes mellitus and another 16 per cent had persistence or recurrence of hypoglycemia after operation. In 6.8 per cent, the hypoglycemia was the result of either unresectable metastatic disease or diffuse adenomatosis, but 9.2 per cent of the patients had tumors that were missed at operation. Undoubtedly these operative failures will be less frequent as new techniques of diagnosis, preoperative localization, and intraoperative monitoring of serum glucose levels gain widespread usage. In general, the long-term outlook for patients after resection of a benign insulinoma is excellent. Streptozotocin therapy is helpful in about 60 per cent of patients with metastatic disease.

CONCLUSIONS

In recent years, significant advances in the diagnosis and preoperative localization of insulinomas have been made. The definitive diagnosis of insulinoma in a hypoglycemic patient is still difficult at times, but new tests such as the measurement of proinsulin and C-peptide and the calcium infusion provocative test aid greatly in selected patients. Undoubtedly, patients with an insulinoma do best when all tumor is resected at the time of initial exploration. Because these tumors are often small, one should attempt to localize them preoperatively since this may aid the surgeon during operation. At present this is done most effectively by angiography; however, the technique of selective pancreatic vein catheterization for hormone analysis appears to be very promising and warrants further investigation. The monitoring of serum glucose concentrations during operation appears to add safety to the operation since

hypoglycemia is prevented. At times this technique may also aid the surgeon in recognizing that an occult tumor has been resected. However, both false negative and false positive responses have been reported. As these new techniques become more widely utilized, the overall success rate of operation will undoubtedly be improved.

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Pancreatic Islet Cell Tumors: Insulinoma, Gastrinoma, and Glucagonoma

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In February 1869 Paul Langerhans, a medical student at the Friedrich Wilhelms University in Berlin, as a candidate for the degree of Doctor of Medicine and Surgery, presented his inaugural dissertation on the microscopic anatomy of the pancreas. He did not speculate on the physiologic function of the islets of cells that now bear his name and, even though the endocrine function of the pancreas was suspected, it was not until the isolation of insulin in 1922 that the role of the pancreas as an endocrine organ was proved. These microscopic multiple cell aggregates, now estimated to number over one million in the human pancreas but to constitute a total of only one gram of tissue, have emerged as intricate endocrine organs elaborating a variety of polypeptide hormones with extensive biologic function (Fig. 1). Although the possible role of the pancreas in diabetes was postulated in the first decade of this century, it was not until 1922 that the endocrine function of the pancreas was proved when insulin was discovered by Frederick Banting,[1] a practicing clinical surgeon, and his colleagues.

During subsequent years, the effects of an overdose of insulin were well documented and descriptions of patients with hypoglycemia and symptoms similar to those observed with insulin overdosage were described.[13] In 1927 Mayo operated upon a patient with severe hypoglycemia and found a pancreatic islet cell tumor with liver metastases.[17] Two years later Graham of Toronto removed a functioning islet cell adenoma from a woman, which cured her attacks of hypoglycemia.[2] The insulinoma syndrome was firmly established when Whipple reported eight cases in 1935.[15]

A second syndrome resulting from islet cell tumors emerged in 1955 with the description by Zollinger and Ellison[20] of two patients with such intractable, recurrent peptic ulcer disease that total gastrectomy became

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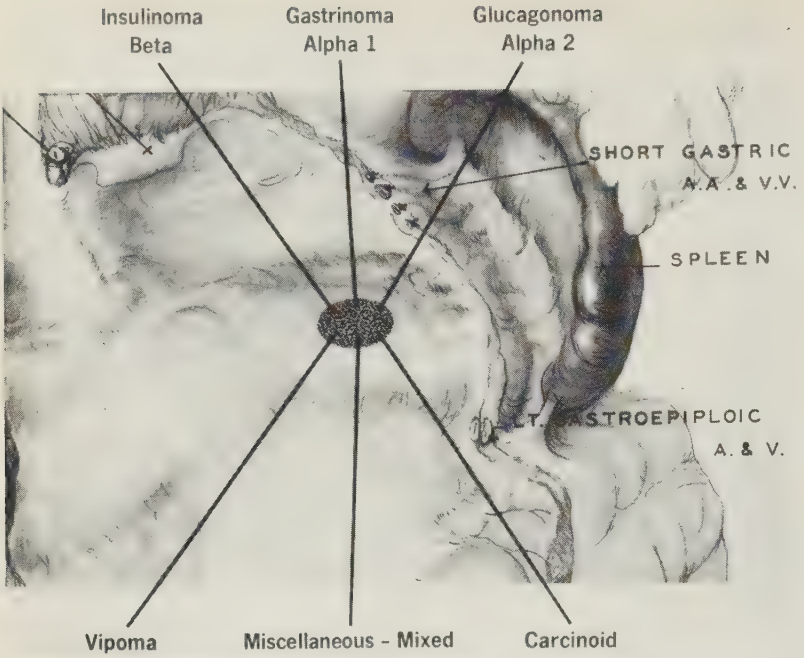

Figure 1. Syndromes resulting from pancreatic islet cell tumors may be highly variable. The three major syndromes are insulinoma from beta cell tumors, gastrinoma from alpha 1 cell tumors, and glucagonoma from alpha 2 cell tumors, with a wide variety of less common clinical pictures produced by other tumors arising from the islet cells.

necessary to prevent recurrent ulceration. Development of a practical method for measuring insulin by Yalow and Berson[19] in 1959 using radioimmunoassay techniques widened the diagnostic and therapeutic vistas immensely, permitting better understanding of a number of clinical syndromes resulting from abnormalities of the various endocrine organs. In addition to insulin, the pancreatic islet cells have been shown to elaborate glucagon, "human pancreatic polypeptide," somatostatin, and possibly others. In addition, many of these polypeptides have components of different molecular weight and much continues to be learned of their nature and function. In 1905 Edkins postulated the presence of a gastric humoral stimulant of acid secretion and proposed the name "gastrin" for this substance. When Gregory[6] found gastrin in the extract of a tumor from a patient who had been operated on for the Zollinger-Ellison syndrome, a new concept of ectopic production of hormones arose, since gastrin has not been found in normal islet cell tissue.

Yet a third major syndrome resulting from islet cell tumors emerged with documentation of the glucagonoma syndrome by McGavran and associates in 1966.[12] Thus, islet cell tumors, either adenoma or carcinoma, may produce a variety of syndromes. The insulinoma syndrome results from tumors involving the beta cells, the gastrinoma syndrome from alpha 1 cells, and the glucagonoma syndrome from the alpha 2 cells. Other miscellaneous syndromes may result from production of other functioning polypeptides by islet cell tumors. In addition, the more compli-

cated multi-endocrine syndromes are emerging in the intriguing concept linking many of these tumors through the shared common characteristics of amine content, precursor uptake, and decarboxylation (APUD). This concept has stimulated the interest and efforts of numerous investigators interested in this field.

LOCALIZATION OF ISLET CELL TUMORS

With ready availability and subsequent refinements of radioimmunoassay diagnostic tehniques, increased awareness and better understanding of these syndromes have evolved. In the past, many patients progressed to widespread local and metastatic disease prior to diagnosis; however, particularly with insulinoma, the surgeon's skill was often severely tested to identify a small tumor in the substance of the pancreas. Recent developments have greatly improved the capacity to localize pancreatic lesions, making it possible to know prior to operation the size and location of the tumor. Increased experience with ultrasonography and computerized axial tomography have greatly improved visualization of pancreatic abnormalities, although these diagnostic methods are somewhat limited, particularly when the tumor is small and of essentially the same density as the pancreas itself. Injection of contrast material such as Gastrografin in the duodenum may be helpful in identifying lesions located in the head of the pancreas. Endoscopic retrograde cholangiopancreatography (ERCP) has not been used to any extent but may be a useful diagnostic aid. Various isotopic scanning methods may be useful in delineating extensive and metastatic tumors.

Angiographic studies of the arterial supply to the pancreas have become increasingly valuable as a localizing mechanism.[3] Rapid developments have permitted careful study of the branches of the celiac axis either as a whole or individually, and tumors less than 1 cm in diameter may be demonstrated using special pharmacoangiographic or superselective techniques. In general, tumors located in the head of the pancreas are more easily visualized than those in the body and tail because of overlying vascular shadows, but special techniques can overcome these problems. With greater angiographic sophistication, one should rarely have to operate without having a good general idea of the location of the tumor. In the event that such techniques fail, Ingemansson and colleagues[8] of Sweden have recently described a method of percutaneous catheterization of the transhepatic portal vein with advancement of the catheter to obtain blood samples from various pancreatic venous tributaries for polypeptide assay. Catheter samples are also obtained from the inferior vena cava and abdominal aorta. Information obtained through this triple catheterization technique has effectively localized both insulinomas and glucagonomas in the hands of these investigators. Further refinement and increased availability of these various studies should greatly remove the hitherto great problem of localization of small islet cell tumors at the time of exploratory operation.

INSULINOMA

Publication in 1935 of case reports of eight patients with islet cell insulinoma treated by Whipple[15] firmly established this entity, and three years later he suggested the diagnostic triad that bears his name: "Symptoms of insulin shock must appear after or before a complete fast is finished; the patient's fasting blood sugar must show a 50 per cent of normal or lower; symptoms of insulin shock must be relieved immediately after the administration of glucose."[16] It is important to remember that hypoglycemia may result from a large variety of causes and that even when Whipple's triad can be demonstrated, the diagnosis is far from certain. Hypoglycemia produced by hyperinsulinism most commonly occurs during the fasting state, as Whipple indicated, often in the early morning, manifested by a state of confusion and inappropriate behavior. Many patients develop a marked tolerance to chronic hypoglycemia and learn to avoid or prevent symptoms by intake of carbohydrates, often with resulting obesity. Symptoms result from two different mechanisms: decreased glucose to the central nervous system and a compensatory release of catecholamines into the blood stream. The neuroglucopenia results in headache, blurred vision, anxiety, hunger, inappropriate behavior, mental confusion, and may progress to stupor, coma, and convulsions; whereas the adrenalin response results in sweating, tremor, pallor, palpitation, and apprehension. It is not infrequent that the manifestations may be attributed to psychiatric problems or the patient may be thought to be under the influence of drugs or alcohol. By 1973, we reviewed over 1000 patients with insulinoma in the English language literature,[4] and since then many additional series have been recorded.

In over 90 per cent of patients with islet insulinoma syndrome, the syndrome results from single adenomas; in the remainder the cause is multiple adenomas of islet cell hyperplasia or carcinoma. A small percentage of these tumors arises in ectopic locations (Fig. 2). Most adenomas tend to remain small (less than 3 cm in diameter) when symptoms become sufficiently severe that surgical attention is sought.

One of the most helpful diagnostic studies is the correlation of the blood glucose level with the plasma insulin level as measured by the radioimmunoassay technique. Hypoglycemia normally depresses insulin release from the islet cells so that the radioimmunoassay level is low in hypoglycemia from most other causes, whereas in the patient with insulinoma, the level of plasma insulin is inappropriately elevated for the low blood glucose level. These studies must be done in the fasting patient.

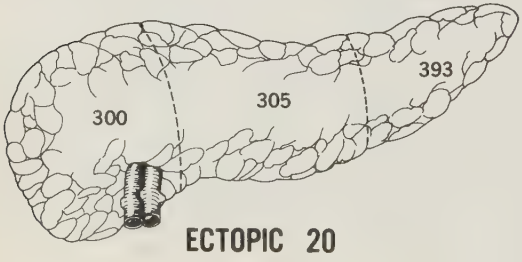

Figure 2. Distribution of 1018 insulinomas collected from a literature review showing approximately equal distribution throughout the pancreas and only 20 appearing in an extrapancreatic location.

A number of other diagnostic studies may be useful. In the diazoxide suppression test the administration of this compound results in an increase in blood glucose by depressing the secretion of insulin. If this occurs in the presence of hypoglycemia, inappropriate secretion of insulin by a tumor is suggested. In addition, diazoxide may be useful in maintaining satisfactory blood glucose levels as a method of treatment. Other studies, such as the tolbutamide tolerance test, the leucine tolerance test, as well as the oral glucose tolerance test, may be helpful. An abnormally high ratio of proinsulin to insulin has been thought by some to suggest a malignant insulinoma. Intravenous injection of exogenous glucagon has also been used as a diagnostic test for insulinoma.

During the preoperative period care should be taken to avoid severe persistent hypoglycemia. In addition, a diazoxide test should be performed to determine if tumor secretion can be decreased by this mechanism. With current diagnostic studies available, exploration can be undertaken with a high degree of conviction that a tumor is present. In addition, the numerous localizing studies now available should make it possible to know in advance where the lesion will be found in a large percentage of patients. Nevertheless, the surgeon must be prepared to expose and examine the entire pancreas, and a liberal incision designed for this purpose should be made. Many of the tumors will be readily visible or palpable and can be easily removed, either by extirpation of the lesion or by distal pancreatectomy, depending upon the location of the tumor. If no lesion is seen, the pancreas must be palpated throughout its extent. This can best be done by freeing the lower border of the peritoneum as well as the head of the organ by mobilizing the duodenum. The pancreas can then be palpated bimanually by placing the fingers in front and behind the mobilized pancreas. If this search is futile, an examination of the wall of the duodenum and the peripancreatic region should be made for an ectopic location of the adenoma. When such a situation arose in the past, blind distal pancreatic resection was the procedure of choice. Current opinion regarding the appropriate course of action in such circumstances varies. If the hypoglycemia was reversible by the administration of diazoxide in the preoperative period, one may elect to avoid blind resections in the hope that subsequent localizing studies may be positive and permit reoperation at a future time. If the insulinemia is not suppressible by diazoxide, distal pancreatectomy should be undertaken and the specimen carefully examined for the presence of a small adenoma or hyperplasia. The tumors are distributed fairly equally throughout the pancreas so that there is at least a 50 per cent chance of removing the tumor with distal hemipancreatectomy. During this procedure the blood glucose level should be monitored carefully, as removal of an adenoma will usually be reflected by rise in blood glucose level. This is far from an absolute finding since other hormones may be released during operation which will cause an increase in blood glucose. Should symptoms persist following this procedure, the patient may be maintained on diazoxide and further localizing studies carried out. There seems to be little or no place for total pancreatectomy at the time of first exploration.

Malignant islet cell tumors with metastases may benefit from the administration of diazoxide, and many of the tumors have responded

dramatically to the administration of streptozotocin or the other anticancer agents.

GASTRINOMA

A new chapter in the islet cell story unfolded in 1955 when Zollinger and Ellison[20] reported two patients with severe ulcer diathesis associated with noninsulin-producing islet cell tumors of the pancreas. Both patients were secreting large volumes of highly acid gastric juice and both had severe ulceration in the jejunum just beyond the ligament of Treitz; one also complained of diarrhea. Both patients were treated by total gastric resection and one was still living and well at last report[21] despite presumed persistence of the pancreatic islet cell lesion. The plot subsequently thickened when development of radioimmunoassay techniques made it possible for Gregory[6] to identify large quantities of gastrin in specimens of islet cell tumors taken from similar patients. At the turn of the century Edkins postulated the presence of a secretogogue in the gastric antral mucosa and designated this substance gastrin; however, gastrin in any of its forms has not been identified as being produced by normal islet cell tissues. By 1974 the Zollinger-Ellison tumor registry had collected over 800 patients,[18] review of which provides general guidelines to be used in the management of this problem.

Gastrin is a heterogeneous group of polypeptides, with different forms having from 13 to 34 amino acid chains. These polypeptides act on receptor sites in the gastric parietal cells with resultant hypersecretion of hydrochloric acid.

The diagnostic triad of the islet cell ulcerogenic syndrome consists of fulminating ulcer diathesis, excessive gastric hypersecretion, and the presence of a non-beta islet cell tumor. Severe acid peptic ulceration may occur in various parts of the duodenum, jejunum, or esophagus and is often manifested as early marginal ulceration after subtotal gastric resection. In approximately 50 per cent of patients, diarrhea of varying degree with accompanying steatorrhea is present, the latter resulting from inactivation of pancreatic fat splitting enzymes in the duodenum by the hyperacidity. Most patients with this syndrome will produce at least one liter of gastric secretion in an overnight 12-hour aspirate containing more than 100 mEq of hydrochloric acid. If the gastrin levels in such patients exceed 1000 pg per ml, the presence of the Zollinger-Ellison syndrome is highly likely. When serum gastrin levels are below this level, various stimulating tests such as simple feeding of a meal with measurement of gastrin levels, calcium infusion tests, the secretin infusion test, and glucagon stimulation may be used as additional diagnostic aids.

Based on early understanding of the syndrome, total gastric resection appeared to be the universal operative procedure of choice and still is for most patients. However, with better understanding of the pathology, the surgeon now has other options depending upon the circumstance. These tumors are generally slow-growing; however, there is an unusually high disposition for multiple primary sites. Approximately 60 per cent have

been found to be malignant, 80 per cent associated with metastases (Fig. 3). Of the 35 per cent of the lesions found to be benign, more than half are multiple. Approximately 6 per cent of patients have islet cell hyperplasia only. As a basic operative principle it is essential to remember that either total gastrectomy or complete removal of functional islet cell tumor is required to halt the fulminant ulcer diathesis, and reliance on tumor excision only may be inadequate since tumors are frequently multiple and may be difficult to locate. In addition, if the tumor is malignant, occult metastases may well be present.

When operating on patients with Zollinger-Ellison syndrome, the first step is a thorough examination of the pancreas and surrounding area in an effort to identify and assess a gastrin-producing lesion. Careful mobilization and bimanual palpation of the entire pancreas, including the head, as well as careful examination of the liver, greater omentum, porta hepatic area, and bowel mesentery for the presence of suspicious lymph nodes, should be carried out, and frozen-section biopsy of suspicious areas made. A sizable number of tumors have been found in the submucosal portion of the duodenal wall, and thorough examination of this area, even through a duodenomyotomy, may be necessary if the lesion is small. Tumor may be found in a lymph node, particularly in the periduodenal or peripancreatic area, without an obvious primary tumor.

If no evidence of tumor is found, then the tail of the pancreas should be resected and examined histologically for islet cell hyperplasia or microadenomatosis. In the absence of a tissue diagnosis of tumor or hyperplasia, total gastrectomy is probably not indicated, but rather vagotomy and hemigastrectomy should be done since hypergastrinemia may result from hyperplasia of the gastrin-producing cells of the antrum. Careful postoperative monitoring of the serum gastrin levels can detect the persistence of gastrin-producing tissues. Cimetidine is an effective histamine H_2-receptor antagonist in suppressing acid secretion and can be

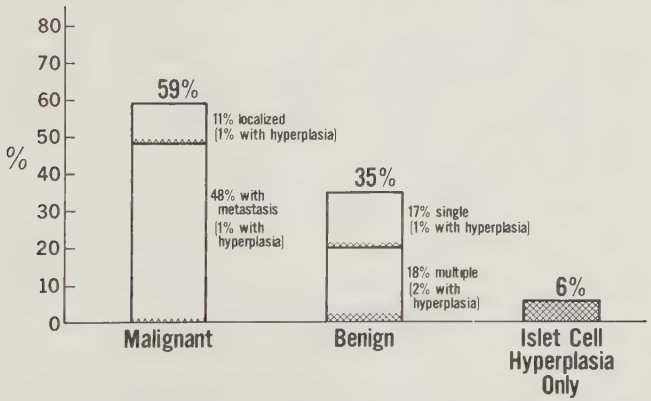

Figure 3. In a large collected series of patients with gastrinoma, 59 per cent of tumors were malignant and a large percentage of both benign and malignant lesions were multiple. Islet cell hyperplasia was reported in 6 per cent of patients and was also present in a small percentage of patients with both malignant and benign gastrinomas. (Redrawn from Wilson, S. D.: Ulcerogenic tumors of the pancreas: The Zollinger-Ellison syndrome. *In* Carey, L. C. (ed.): Pancreas. St. Louis, C. V. Mosby Co., 1973.)

used to treat such patients and to avoid complications if subsequent total gastrectomy is indicated. To avoid complications, some authors recommend total gastrectomy even in the absence of a positive tissue diagnosis, especially in patients with extremely high preoperative serum gastrin levels.

Approximately 13 per cent of the registry patients had identifiable duodenal wall tumors. Local excision of these tumors without total gastrectomy was successful in only a small number of patients and should be attempted only when metastases, associated pancreatic lesions, or islet cell hyperplasia have been ruled out.[14] Total gastric resection, accompanied by excision of tumor if feasible, has resulted in over a 50 per cent long-term survival. Inhibition of further tumor growth and development following total gastric resection as reported by Friesen[5] is apparently an infrequent occurrence. Regression of these tumors following administration of anticancer drugs, particularly streptozotocin, has been reported. In addition, the development of the histamine H_2-receptor antagonist drugs (Cimetidine), which provide a pharmacologic blockade of the receptor site, raises the question of protecting the end organ stomach, with the intriguing possibility that sacrifice of the stomach may be prevented by the combination of pharmacologic and cytotoxic medications.[11] Extended follow-up of patients being treated in this fashion may well alter the surgical approach to patients with Zollinger-Ellison syndrome.

GLUCAGONOMA

The third major clinical syndrome associated with islet cell tumors results from the elaboration of glucagon and is sometimes referred to as the hyperglycemic, cutaneous syndrome because of the two major clinical features. Glucagon was identified and named in 1923 by Kimball and Murlin[9] who recognized its property of increasing blood glucose levels. There was considerable interest in the physiologic properties and therapeutic potential of glucagon during subsequent years; however, it was not until 1966 that McGavran and associates[12] described the prototype patient, which established the glucagonoma syndrome as an entity. Study of this and subsequent patients was greatly facilitated by the ability to measure glucagon by radioimmunoassay techniques. In 1974 Mallinson and co-workers[10] from Guy's Hospital in London studied nine patients and delineated the major features of the syndrome: diabetes mellitus, characteristic skin lesions (necrolytic migratory erythema), glossitis, normochromic, normocytic anemia, and weight loss, with associated elevation of the plasma level of immunoactive glucagon.

A literature review in 1978[7] revealed 47 case reports of the glucagonoma syndrome, six of which had been reported prior to the McGavran publication, and additional case reports continue. Patients in this series were between the ages of 20 and 73 years with a sex ratio of 28 females to 19 males (Table 1). Most patients had significant weight loss even when the lesion was comparatively small, consistent with the catabolic nature of glucagon. In many instances the tumor was extensive

Table 1. *Clinical Features of 47 Patients with Glucagonoma**

	YES	NO	?
Diabetes	44	2	1
Necrolytic migratory erythema	36	5	6
Glossitis	16	9	22
Normochromic, normocytic anemia	30	3	14
Weight loss	34	1	12
Elevated glucagon	37	0	10
Hypoaminoacidemia	11	0	36
Metastases	27	18/3	2

*The sex ratio is 28 females to 19 males. Age ranges from 20 to 73 years (mean, 56 years). As noted in the third column, no mention of many of the clinical features was made in several reports. Of the 18 patients found not to have metastases at the time of diagnosis, three subsequently developed metastases following surgical resection of the primary lesion.

and metastases were evident at the time of diagnosis, although in 18 of the reported patients the tumor was noted to be confined to the pancreas. In at least three of these patients, metastases occurred at a later date. From the descriptions of the tumor it would appear that the majority arose in the body and tail of the pancreas (Fig. 4), although it should be remembered that this was also thought to be true for insulinoma until a large number had been reported. All tumors on which careful microscopic studies were made were alpha 2 type islet cells.

The characteristic skin lesion in these patients is a necrolytic, migratory erythema that has led to diagnosis in most of the recent cases reported. There is a characteristic evolution of individual lesions over 7 to 14 days, progressing from erythematous macules to blisters, central necrosis, crusted lesions with erythematous margins, followed by central clearing and scaling. Lesions occur most frequently in areas of friction such as the buttocks, perineum, groins, perianal area, natal cleft, lower legs, hands, feet, or perioral areas. Biopsy specimens from the peripheral areas of these lesions show characteristic changes in the superficial

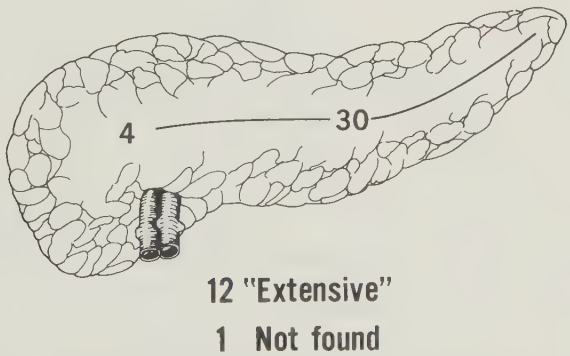

Figure 4. Distribution of tumor in the 47 patients with glucagonoma, indicating what appears to be a more common location in the body and tail of the pancreas. This was also thought to be true for insulinoma before a large number was collected. In 12 instances the primary lesion was so massive that origin was not clear and in one instance the primary tumor was never found.

epidermis. There is also an associated glossitis or stomatitis in many patients. The mechanism of the cutaneous features of the syndrome is not clear.

The majority of patients have frank diabetes or a diabetic glucose tolerance test, mostly controllable by diet or small doses of insulin. No instances of ketoacidosis were described, even though two patients were insulin resistant. In all patients for whom glucagon levels were reported, a significant elevation was found, either in plasma or in the tumor itself. An additional feature is a decreased plasma amino acid level in the 11 patients evaluated for this factor. Normochromic, normocytic anemia has been an almost constant feature of patients carefully documented, and appears to be independent of the nutritional depression of most patients with advanced malignancy, possibly resulting from the general catabolic action of glucagon.

Pathologic Physiology

Glucagon is a single chain polypeptide secreted by the alpha 2 cells of the pancreas, and in its circulating form exists in at least four different molecular weight patterns. Although primarily active in the regulation of plasma glucose concentration, it also plays a role in protein and fat metabolism, exerting a catabolic action in each case. In conjunction with its antagonist, insulin, glucagon plays the primary role in regulating nutrient balance by adjusting the anabolic-catabolic ratio of the organism. Evidence suggests that insulin plays the primary role in regulating normal fuel utilization, whereas glucagon exerts its function more prominently during the fasting state and following a heavy protein meal to prevent hypoglycemia that might result from inappropriate insulin response in the absence of carbohydrates. Glucagon functions primarily in the liver to stimulate glycogenolysis as well as gluconeogenesis, and it has been suggested that it also exerts a lipolytic action in fat cells. Elevated glucagon levels occur during surgical procedures, in acute illnesses, with severe burns, and during exercise. Glucagon degradation occurs in the kidney as well as in the liver, and patients with chronic renal or hepatic failure often have elevated glucagon levels. Although the biologic significance of the various fractions of circulating glucagon is not entirely clear, it has been suggested that the 9000 dalton molecular fraction may represent proglucagon and its presence may indicate an underlying glucagonoma.

Treatment

If the diagnosis is made while the tumor is still localized, surgical resection can be curative. Unfortunately, in only 15 of the reported 47 patients was this possible, and in at least 3 of the patients recurrent tumor developed postoperatively. As in the other islet cell tumors, even when malignant, these tumors tend to be extremely slow growing. Effective treatment with chemotherapy, using streptozotocin, has been reported with increasing frequency. Another chemotherapeutic agent, diamino triazeno imidazole carboximide (DTIC) has been used successfully in a patient who showed no response to streptozotocin. L asparaginase and

other anticancer drugs have also been used. There is also a suggestion that somatostatin or one of its analogues may be effective in suppressing production of glucagon by the tumor, and it seems likely that other methods of inhibiting glucagon secretion may become available.

Through better awareness of the syndrome, earlier diagnosis at a stage when surgical resection is possible should occur with greater frequency. Even when metastases have occurred, excellent palliation from chemotherapeutic drugs can result in prolonged symptom-free survival.

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Uncommon Tumors of the APUD System

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Within the last 10 years there has been a virtual explosion of information relating to new hormones, their cells of origin, and newly described clinical syndromes resulting from their excessive secretions. From a biologic point of view, some have been known for over 70 years (secretin and gastrin) but it is only recently that many of these polypeptide hormones have been isolated, synthesized, and chemically identified for quantitative measurements by radioimmunoassay techniques. The "breakthrough" investigations that clarify our understanding of the significance of polypeptide and amine hypersecretions include: description of the APUD concept which links the common cytochemical characteristics of *A*mine *P*recursor *U*ptake and *D*ecarboxylation to the derivation of these cells in the embryonic neuroectoderm; the immunofluorescent localization of the cells and the radioimmunoassay of the content of the polypeptides in tissues and serum; and the findings that some of the polypeptide hormones have been found in both the brain and in the gut, thus unifying the humoral and neural components of homeostasis back again into a neuroendocrine system.[6] For some polypeptides the specific physiologic and biologic effects are still not known precisely; others have been linked etiologically to specific clinical syndromes, many of which are described in this issue. In this article some of the more unusual and rare syndromes are briefly described mnemonically, wherever possible, according to their primary clinical pictures within the APUD concept and according to the present state of our knowledge.

DIARRHEOGENIC SYNDROMES

A number of hypersecretory states, excluding local gastrointestinal pathologic conditions, are associated with the symptom of diarrhea for a variety of physiologic reasons. Notable among these is the steatorrhea

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usually seen in patients with the ulcerogenic (Zollinger-Ellison) syndrome, which is accountable to the massive acidification of the duodenum and small intestine; in these instances diarrhea ceases when gastric acid hypersecretion is controlled by total gastrectomy or effective cimetidine therapy. Other neurohumoral hypersecretion states include the carcinoid syndromes of foregut and midgut varieties, the watery diarrhea, hypokalemia, and achlorhydria (WDHA or Verner-Morrison) syndrome associated with vasoactive intestinal peptide (VIP), prostaglandin, and perhaps other secretin-like elaborations, and the very rare syndromes caused by cholecystokinin-pancreozymin (CCK-P) hypersecretion, and possibly gastric-inhibiting polypeptide (GIP) and human pancreatic polypeptide (HPP) release.

Carcinoid Syndromes

Diarrheogenic syndromes that occur as a result of functioning carcinoid tumors vary in their clinical presentation depending on their primary location. The classic presentation is that of midgut origin, usually a tumor of the ileum, with metastases to the liver. Its metabolic humoral substances are released systemically, bypassing deamination in the liver. In such situations the humoral products from the malignant enterochromaffin (EC) cells are amines, primarily serotonin. More bizarre (atypical) carcinoid syndromes are observed when the primary tumor originates in the foregut (down to and including the pancreas and duodenum); in such instances there may be elaboration of polypeptides in addition to the amines 5-hydroxytryptamine and histamine.

Carcinoid tumors can arise in any part of the endoderm from cells that are embryologically derived from neuroectoderm. Three-fourths of all abdominal carcinoid tumors are of midgut origin: 45 per cent from the appendix and 28 per cent from the small intestine, usually the ileum.[25] Carcinoid tumors are, in fact, the most common primary tumors of the small intestine. The rectum (hindgut) is the third most common site of origin, constituting 16 per cent of reported cases. Of the foregut carcinoid tumors (lung, stomach, duodenum, and pancreas) bronchial tumors are the most frequent and represent approximately 10 per cent of the total number. On rare occasions, carcinoid tumors have been reported to arise in ovarian and testicular teratomas. Approximately 20 per cent of carcinoid tumors are multiple and may be found in association with the more frequent carcinomas of the gastrointestinal tract.

CLASSIC CARCINOID SYNDROME (MIDGUT VARIETY)

Clinical Picture

Diarrhea is the hallmark of this "functioning syndrome," and is usually the most disabling part of the disease. It frequently accompanies or follows episodes of flushing and is characterized by borborygmi, urgency, and frequent passage of explosive, watery stools.

Cutaneous flushing is an early symptom in most patients having midgut tumors with hepatic metastases. Hypotension and other vasomotor changes may be associated with episodes of flushing.

Venous telangiectasia develops in approximately 50 per cent of patients at some time during the course of their disease. They are most prominent over the nose, upper lip, and cheek, giving rise to a "butterfly" pattern.

Endocardial lesions are found in 50 per cent of patients with the classic carcinoid syndrome. These are characterized by deposition of fibrous tissue, similar to collagen, on the endocardium and valve cusps, causing distortion of valve cusps, chordae tendineae, and papillary muscles, and leading to interference with valve function. In the classic midgut variety of the syndrome, the endocardial lesions are most common in the right side of the heart, producing right heart failure owing to tricuspid incompetence and pulmonary stenosis.

Bronchial constriction leading to signs and symptoms similar to asthma is seen in 10 to 20 per cent of patients with the midgut variety of the carcinoid syndrome.

Pellagra develops in 5 per cent of patients with the "functioning syndrome." It is thought to be caused by exaggerated serotonin production which decreases availability of tryptophan for niacin biosynthesis.

Hepatomegaly and *hyperactive bowel sounds* are common. Carcinoids of gastrointestinal origin drain into the liver by way of the portal system. Since the liver metabolizes most of the serotonin to which it is exposed, the "functioning syndrome" does not occur from a gastrointestinal primary tumor until massive liver replacement by tumor has occurred.

ATYPICAL CARCINOID SYNDROMES (FOREGUT VARIETY)

The syndrome associated with *bronchial carcinoid* tumors is characterized by prolonged, severe flushing attacks of a deep red color which may persist up to three or four days. Periorbital and facial edema frequently develops. Marked lacrimation, salivation, sweating, temperature elevation, and tachycardia are common. Anxiety and disorientation may precede the attack. Prolonged flushing attacks are accompanied by diarrhea, nausea and vomiting, asthma, and hypotension. Left-sided endocardial lesions give rise to mitral and aortic valve disease, with associated left-sided heart failure and pulmonary edema. Bronchial carcinoids tend to be more aggressive than are their midgut counterparts. Widespread metastases are common. Like all other foregut carcinoid tumors, bronchial carcinoids frequently elaborate other polypeptide hormones, producing clinical pictures of superimposed endocrinopathies.

The syndrome caused by *gastric carcinoid tumors* may be associated with a distinctive flush that begins as vivid red patches with sharply defined, serpentine borders. As time passes, the borders become confluent. Flushes often begin after meals.

Pancreaticoduodenal carcinoid tumors produce syndromes that are

notorious for their associated or primary polypeptide elaboration from gastrinomas, glucagonomas, insulinomas, and so on, which may mask the carcinoid syndrome completely.

Pathophysiology

Enterochromaffin cells, derived from the neural crest,[19] are ubiquitous in the gastrointestinal tract (including the pancreas), bronchial epithelium, and urogenital tract. Their common origin and common cytochemical and ultrastructural characteristics establish their place in the APUD system.

The biosynthesis of serotonin takes place almost exclusively in the enterochromaffin cells. Other APUD cells and some elements of the central nervous system contribute a small amount. In the enterochromaffin cell, the amino acid tryptophan is metabolized to serotonin (5-HT). Under normal circumstances, 1 to 2 per cent (5 to 10 mg) of daily ingested tryptophan is converted to serotonin. In patients with the carcinoid syndrome, however, up to 60 per cent of ingested tryptophan may be shunted down this pathway.

Bradykinin, a 9 amino acid polypeptide, has been shown to be elevated in the serum of some patients with carcinoid syndrome. It is one of the most potent vasodilators known; it stimulates intestinal motility and can cause bronchoconstriction. Some carcinoid tumors have been shown to contain kallikrein, the enzyme that converts kininogen to bradykinin. Histamine and ACTH have also been reported to be involved in the carcinoid syndrome.

Diagnosis

Many carcinoid tumors are asymptomatic at the time of their discovery. An ovarian or testicular tumor may be discovered on routine physical examination or a submucosal mass may be found on rectal examination. A routine chest x-ray film may disclose a lung nodule or a superior mediastinal mass. Other carcinoid tumors become symptomatic prior to onset of the "functioning syndrome," being discovered at the time of laparotomy for intestinal obstruction or intussusception.

The humoral hallmark of the carcinoid syndrome is overproduction of 5-hydroxyindoles, leading to increased urinary excretion of 5-hydroxyindolacetic acid (5-HIAA). Normal values range from 2 to 9 mg per 24 hours in most laboratories. Levels above 20 mg are considered to be diagnostic. Serotonin, histamine, prostaglandin, and bradykinin measurements are available in special laboratories.

Some foregut carcinoid tumors lack the enzyme decarboxylase. Patients with such tumors may excrete increased amounts of urinary serotonin and 5-HTP, in addition to increased 5-HIAA levels. Serotonin and 5-HTP can be measured by paper chromatography. Thus measurement of urinary metabolites may aid in localization of the tumor. Foregut origin may also be suspected if screening for routine polypeptide hormones discloses gastrin, glucagon, ACTH, or thyrocalcitonin (TCT) elevations.

Certain provocative tests may be of value when a carcinoid syndrome is suspected. Massage of the tumor or the enlarged liver may induce an

attack of symptoms. Kaplan reported induction of typical carcinoid attacks in response to calcium infusion.[12] In his studies, blood serotonin levels increased markedly and correlated well with the onset of the attack. Another provocative test, to be used cautiously and only when it is considered necessary, is the epinephrine infusion test which is known to reproduce flushing in most but not all patients with carcinoid syndromes who flush spontaneously.[12]

Treatment

Aggressive surgical treatment constitutes the primary option for cure and/or palliation in patients with carcinoid tumors, with or without symptoms of the syndromes. Even in the presence of widespread metastatic disease, exploration is important because the removal of all resectable tumor may frequently result in significant palliation. Local resection is adequate for benign carcinoid tumors. Wide resection, including lymph node–bearing tissues and partial hepatectomy, when possible, is the treatment of choice for malignant metastatic lesions. Hepatic dearterialization has recently been reported to be beneficial in some patients.[17] Chemotherapeutic agents such as streptozotocin, cyclophosphamide, methotrexate, and 5-fluorouracil, given intraarterially or intravenously, have been used with benefit.[3, 18]

Anesthesia presents no particular problem in the patient with a nonfunctioning carcinoid tumor. In the patient with carcinoid syndrome, however, a number of paradoxical reactions can lead to tragic consequences. Most of these are related to tumor release of serotonin, bradykinin, and other substances during induction and maintenance of anesthesia. Administration of beta adrenergic receptor antagonists and anesthetic agents known to stimulate release of endogenous catecholamines should be avoided. Use of such agents may be followed by profound flushing and hypotension sometimes referred to as "bradykinin shock." Hypotension will most likely be caused by vasodilation and should respond to administration of colloids and crystalloids. If a vasoconstrictor agent is required, alpha receptor agonists are the drugs of choice since they will not induce flushing.

Radiotherapy for remaining, nonresectable hepatic metastases may rarely be of symptomatic benefit.

Pharmacologic therapy may provide some relief for certain symptoms of the carcinoid syndrome.[12] *Diarrhea* will frequently respond to sufficient doses of the usual antidiarrheal narcotic preparations. Methysergide (Sansert), a serotonin antagonist, cyproheptidine (Periactin), an antiserotonin and antihistamine drug, parachlorophenylalanine (PCPA), an inhibitor of tryptophan hydroxylase, and 5-fluorotryptophan, an experimental 5-hydroxytryptophan analog, have all been shown to be of benefit in some patients. All should be used with caution since harmful side effects may outweigh the benefits. *Flushing* is generally not benefited by antiserotonin drugs. Phenoxybenzamine (Dibenzyline) and phenothiazines (Thorazine) are somewhat effective. Glucocorticoids may be helpful in reducing the frequency and severity of flushing attacks caused by bronchial carcinoids. They are of little value in other sites of origin. Methyldopa (Aldomet), a decarboxylase inhibitor, may provide

relief in patients with carcinoid tumors that secrete substantial amounts of 5-hydroxytryptophan. Parenteral use of epinephrine and isoproterenol should be avoided in the treatment of bronchoconstriction because of their known ability to induce episodes of flushing. Inhalation of these agents may be beneficial, but should be used with extreme caution.

Godwin, in a review of 2837 cases of carcinoid tumors, clearly showed that survival is related to site of origin, tumor size, state of disease at the time of treatment, and adequacy of resection.[8] Locally invasive tumors had a five-year survival of 94 per cent, ranging from 75 per cent for small bowel lesions to 99 per cent for those originating in the appendix. Regional lymph node involvement decreased five-year survival to 64 per cent. A high incidence of associated APUD tumors, multiple endocrinopathies, and other malignancies is reflected in the prognosis.

Chronicity of symptoms and a slow rate of growth is the nature of these tumors. Perseverance in treatment of patients with carcinoid tumors, even in the face of widespread metastatic disease, can be rewarding to both the patient and the physician.

WATERY DIARRHEA, HYPOKALEMIA, ACHLORHYDRIA (WDHA) SYNDROME

Verner and Morrison, in 1958, described two patients who died of renal and metabolic consequences of watery diarrhea, hypokalemia, and uremia.[22] Since that time at least 85 well documented cases of WDHA syndrome have been reported. The average age of these patients is 47 (range 5 to 72) and 65 per cent have been female.

Clinical Picture

The presenting complaint is almost invariably watery diarrhea. At first the diarrhea is intermittent in nature. The symptomatic periods gradually become more frequent, eventually coalescing to form a picture of unrelenting watery diarrhea, often explosive. Passage of 10 to 15 stools a day is usual, with an average total volume of 4.6 liters (range 3 to 10 liters). The stools are described as having the color of weak tea, and are rich in electrolytes and bicarbonate. The diarrhea is purely secretory. Gastrointestinal hypermotility and abdominal cramping are unusual. Malabsorption and steatorrhea are uncommon.

The diarrhea, with its resultant fecal loss of water, potassium, and bicarbonate, is responsible for the features that make patients with this syndrome so difficult to manage. Symptoms of muscular weakness, lethargy, nausea and vomiting, and crampy abdominal pain are caused by potassium depletion and are usually relieved by potassium replacement. Dehydration is a major problem and most patients have a significant component of prerenal azotemia.

Verner and Morrison report that 59 per cent of patients tested had basal achlorhydria.[23] Half had no secretory response to histamine. Gastric biopsies invariably show normal parietal cells. Gastric acid secretion returns to normal following resection of diarrheogenic tumors.

Flushing, resembling that induced by carcinoid tumors, has been reported in 14 patients. Only two of these patients have had documented elevations of serum serotonin or urinary 5-HIAA levels.

Hypercalcemia has been reported in 18 of 37 patients collected by Verner and Morrison. The excess calcium is thought to originate from bone, directly induced by the diarrheogenic tumor. Serum phosphate levels are usually normal and parathyroidectomy has been uniformly unsuccessful in relieving the hypercalcemia. Tetany owing to associated hypomagnesemia has been reported.

Pathophysiology

In this diarrheogenic syndrome, as a result of tumor elaboration of a secretin-like hormone, the end organ is the mucosa of the small intestine in which there is active exocrine secretion such that the volume of fluid leaving the distal ileum is 10 times normal. The volume and composition of intestinal fluid reaching the ligament of Trietz are normal; thus nasogastric suction does not alter the diarrhea in WDHA. Diarrhea results because the volume of fluid exceeds the resorptive capacity of the normally functioning colon. Bicarbonate concentration of this fluid is especially high; bicarbonate loss in the stool leads to acidosis. Under the influence of secondary aldosteronism, potassium is exchanged for sodium within the colon, leading to potassium loss in the stools and resultant hypokalemia.

Of 54 patients reported by Verner and Morrison, 43 (78 per cent) had non-beta islet cell tumors of the pancreas.[22-24] Twenty-three of these were benign adenomas. Eleven were caused by islet cell hyperplasia (including nesidioblastosis). Twenty of the tumors were malignant at the time of laparotomy. Approximately 10 per cent of secretory tumors are in extrapancreatic tissues, particularly retroperitoneal ganglioneuromas, adrenal medulla, and rarely, bronchogenic carcinomas. All of these are embryonic sites of APUD cells.

Of the many agents incriminated, *vasoactive intestinal polypeptide* (VIP) appears to be the most likely causative humoral agent. VIP is a member of the glucagon-secretin family of hormones. It is found in discrete endocrine cells of the gastrointestinal mucosa (H cells) where it appears to act as a local tissue hormone (paracrine system). High concentrations of VIP have been found in the autonomic nervous system. Biologic actions of VIP include stimulation of intestinal secretion leading to diarrhea, peripheral vasodilation (flushing), hypercalcemia, inhibition of gastric secretion and motility (like GIP), augmentation of bile flow, stimulation of pancreatic bicarbonate secretion (like secretin), hyperglycemia owing to increased glycogenolysis (like glucagon), and stimulation of glucagon and insulin release. Elevated levels of serum VIP have been reported in a large number of patients with WDHA syndrome. Serum VIP levels also appear to correlate well with disease activity, falling rapidly after resection of the causative tumor and with steroid or streptozotocin-induced alleviation of diarrhea.

A second potential causative agent is prostaglandin E_2 (PGE_2). Of 23

patients with WDHA reported by Jaffe and Condon,[9] ten patients had elevated levels of PGE_2. Five of these patients had normal VIP levels. Diarrhea resolved when PGE_2 levels fell to normal with tumor resection. Known biologic activities of PGE_2 include secretory diarrhea, flushing and vasodilation, hypercalcemia, hypochlorhydria, and hyperglycemia.

Diagnosis

The diagnosis of WDHA should be entertained in the differential diagnosis of any patient with chronic watery diarrhea of large proportions. Concomitant findings of hypokalemia (2.1 mEq per liter is usual) and acidosis (admitting pH of 7.1 is common) should make one suspicious. Specific assays of VIP, PGE_2, and PP are indicated in the diagnostic work-up of chronic watery diarrhea. A method of intestinal perfusion has recently been described by Krejs et al.[14] as a specific diagnostic modality for the diagnosis of intestinal hypersecretion.

Once the diagnosis of secretory diarrhea has been made, tumor localization should be attempted. Because 70 per cent of patients with WDHA have pancreatic tumors, the use of computerized tomography and superior mesenteric arteriography is indicated. Kidney and chest roentgenograms with tomograms may be of value in locating another 10 per cent of tumors. Exploratory laparotomy for diagnosis is frequently necessary.

Treatment

The definitive treatment of secretory diarrhea is surgical excision of the hypersecretory neoplasm or hyperplasia. Preoperative preparation is exceedingly important and consists primarily of careful management of fluid and electrolyte abnormalities. Of the 85 cases reported, seven (approximately 10 per cent) died preoperatively.

With the patient in fluid and electrolyte balance, surgical resection of the hormone-secreting tumor or a subtotal excision of the hyperplastic pancreas (islet cell nesidioblastosis) is the only effective means of cure or gaining long-term remission. Palliative resection of malignant lesions can provide remission and relief of symptoms.

Eighty per cent of tumors responsible for WDHA are found in the body and tail of the pancreas. Most are greater than 3 cm in diameter and are easily identifiable. Only rarely will more than one adenoma be present.

If one is unable to locate a tumor, subtotal pancreatectomy is indicated. Eight of 11 reported patients were "cured" by this procedure.[10] Several, however, required total pancreatectomy for complete relief.

Neither radiation therapy nor 5-fluorouracil have been consistently effective in controlling the growth of malignant diarrheogenic tumors. Kahn et al. reported good relief of symptoms in two patients following intraarterial infusion of streptozotocin.[11]

In seven of 12 patients, adrenal corticosteroids have provided control of diarrhea.[9] Treatment with indomethacin has been followed by dramatic relief of diarrhea in one patient with WDHA caused by PGE_2.[10]

Diarrheogenic Syndrome Caused by Medullary Carcinoma of the Thyroid

Clinical Picture

Medullary carcinoma of the thyroid is presented in another article of this volume, but is briefly mentioned here because diarrhea is present in 30 per cent of patients with medullary carcinoma of the thyroid. The diarrhea, which generally occurs in association with large lesions, clears with resection of the tumor.

Pathophysiology

The mechanism of action is related to the humoral product of the thyroid C cells, thyrocalcitonin, which causes jejunal secretion of water and electrolytes. The C cells (parafollicular cells) are charter members of the APUD system, as are the adrenal medullary cells, which accounts for the association of medullary carcinoma of the thyroid in two multiple endocrinopathies, MEN II and MEN IIb. In addition to thyrocalcitonin, medullary tumors of the thyroid are known to produce prostaglandins, serotonin, histamine, and ACTH, most of which have been implicated in the mechanism of the diarrhea.

Treatment

The primary treatment is surgical excision.

Diarrheogenic Syndrome Caused by Cholecystokinin-Secreting Hyperplasia

Clinical Picture

The only case of a cholecystokinin-secretin APUDoma was reported by Wilson in 1973.[26] The syndrome consisted of diarrhea and severe gastric hypersecretion owing to islet cell hyperplasia. Serum cholecystokinin levels were found to be three to four times normal. Serum gastrin levels were consistently normal or low. In contrast to the Zollinger-Ellison syndrome, secretin infusion failed to raise serum gastrin levels. Basal volume of pancreatic bicarbonate was increased, as was secretin-induced pancreatic bicarbonate secretion.

Pathophysiology

Cholecystokinin is a secretin-like hormone. The actions of cholecystokinin include stimulation of gallbladder contraction, stimulation of pancreatic enzyme secretion, and stimulation of gastrointestinal smooth muscle. In the case reported by Wilson, the diarrhea was found to be primarily related to increased gastric and pancreatic secretion. Excessive small bowel secretion was not found to play a role in the syndrome.

Diagnosis

Wilson postulated that elevated cholecystokinin levels, taken after a test meal, should make one consider a cholecystokinin-secreting APUDoma in the differential diagnosis of chronic diarrhea.

Treatment

At laparotomy pancreatic islet cell hyperplasia was found. Resection of the distal pancreas was curative.

DIARRHEOGENIC SYNDROME CAUSED BY GASTRIC INHIBITORY POLYPEPTIDE-SECRETING TUMORS

Clinical Picture

In 1972, Elias et al. reported a single patient with watery diarrhea, low gastric acid secretion, and hypokalemia caused by a gastric inhibitory polypeptide (GIP)-secreting APUDoma.[5] No other GIP-secreting tumor has been reported to date.

Pathophysiology

Gastric inhibitory polypeptide is a 43 amino acid polypeptide hormone with amino acid sequences in common with glucagon and secretin. The highest concentration of K cells secreting GIP is found in the jejunum. Significant amounts are also found in the duodenum and upper ileum.

Serum concentrations of GIP increase after a test meal. The most potent stimulators of GIP are carbohydrates and fats. GIP produces achlorhydria more certainly than does VIP; it inhibits gastric acid secretion stimulated by pentagastrin, gastrin, insulin, and histamine. It also inhibits pepsin secretion and is a potent stimulator of insulin secretion.

Treatment

At laparotomy a non-beta islet cell tumor was removed from the tail of the pancreas. There were multiple hepatic metastases.

DIARRHEOGENIC SYNDROME ASSOCIATED WITH PANCREATIC POLYPEPTIDE ABNORMALITIES

Clinical Picture

Diarrhea may be a symptomatic feature of pancreatic abnormalities consisting of islet cell hyperplasia or tumor composed of pancreatic polypeptide (PP)-secreting F cells. A characteristic clinical picture has not become clear as yet, but four patients have been described who exhibit definite PP-secreting cell abnormalities, with or without evidence of hyperfunction. Tomita et al. described two patients, one of whom had persistent watery diarrhea that was associated with atypical pancreatic islets composed exclusively of PP-secreting F cells.[21] The other patient, without diarrhea, demonstrated high levels of circulating PP with an exaggerated response to food owing to pancreatic F cell hyperplasia (nesidioblastosis); this patient also had metastatic gastric carcinoma. Bordi et al. reported a case of proven PP tumor of the pancreas in a patient with chronic duodenal ulcer.[2] Ebeid et al. have reported a patient with PP tumor that invaded the papilla of Vater, producing biliary obstruction.[4]

Pathophysiology

Pancreatic polypeptide was isolated by Kimmel during investigations for the purification of insulin.[13] F cells, which contain and presumably secrete PP, are found in the islets and other interstitial areas of the pancreas. Its physiologic role in humans is not clearly identified, yet it appears to be related to digestive processes. Infusion of PP does not produce diarrhea; however, PP levels have been found to be elevated in the WDHA syndrome and may thus be a tumor marker for that syndrome.

OTHER APUD CELL TUMORS AND SYNDROMES

Somatostatinomas (The Inhibitory Syndrome)

Clinical Picture

Somatostatinomas are extremely rare APUDomas. To date, only two cases have been reported in the literature.[7, 15] Both patients were middle-aged women found to have a pancreatic mass at the time of cholecystectomy. In these patients a D cell islet tumor produced SST-like immunoreactivity and bioactivity. These two patients suggest a syndrome consisting of adult onset diabetes mellitus, abdominal pain, suspected gallbladder dysfunction, hypoinsulinemia, and hypoglucagonemia.

Pathophysiology

Immunofluorescent techniques have shown somatostatin to be located in the hypothalamus, the rest of the brain, and in the D cells of the gastrointestinal tract and pancreas. In man, the largest number of SST cells are found in the antral mucosa.

In pharmacologic doses, SST is a potent inhibitor of release of growth hormone, insulin, gastrin, cholecystokinin, VIP, motilin, and TSH. These inhibitory influences may be responsible for the clinical picture seen in the two reported patients, including inhibition of gallbladder contraction (stasis and stones), goiter, delayed gastric emptying, decreased gastric acid output, and steatorrhea. Interestingly, SST has been shown to suppress VIP production by VIPomas with a concomitant reduction in small intestinal secretion.[16]

Pharmacologically, relatively high blood levels of SST are required to produce its inhibitory effects. It is also very rapidly cleared from the circulation (half-life of one minute). In the pancreatic islets, SST-containing D cells are situated between glucagon-secreting A cells and the central mass of insulin-secreting B cells. This arrangement could permit direct local restraint, by somatostatin, upon secretory activities of neighboring cells (paracrine system).

Diagnosis

The diagnosis is unlikely to be made preoperatively. The association of adult onset diabetes mellitus and cholelithiasis is common and unlikely to influence physicians to undertake further, highly sophisticated diagnostic investigations. Measurement of serum SST levels is investigational in special laboratories at this time.

Treatment

The treatment was surgical in both cases.

PARAGANGLIOMAS

Clinical Picture

The presenting complaints are sustained or paroxysmal hypertension and other pheochromocytoma-like symptoms which are discussed elsewhere in this issue.

Pathophysiology

The symptom complexes are produced by catecholamine release from tumors arising in tissues, excepting the adrenal medulla. Reported sites include the carotid body, vagal body, glomus jugulare (four minute glomera of chemoreceptor tissue located in and about the temporal bone), aortic body, ciliary body, autonomic ganglia, "organ of Zuckerkandl," and even tumors occurring in minute subpleural nodules. Their origin has been attributed to neural crest derivatives occurring as nests of chromaffin tissue in or adjacent to autonomic ganglia and their nerves.

Diagnosis

Paragangliomas are most frequently located about the head and neck. A mass may be present and can produce pressure on contiguous structures. The signs and symptoms of these tumors, when hyperfunctioning, are similar to those of pheochromocytomas. When an adrenal medullary tumor is not found, the search must include the various sites of chemoreceptor glomera as rare, potential locations for catecholamine-producing tumors. Tomography and cautious arteriography may be helpful for localization.

Treatment

These tumors are generally biologically benign, and surgical excision is usually curative. The same precautions used in the excision of pheochromocytoma must be taken. Some are extremely large and vascular at the time of operation.

DIFFUSE APUDOMA (MASTOCYTOSIS SYNDROME)

Clinical Picture

The signs and symptoms of diffuse APUDoma are the result of the systemic release of histamine (and possibly heparin) by mast cells. Common symptoms include flushing, tachycardia, episodic severe diarrhea, and headaches. Other symptoms include intestinal malabsorption, hepatosplenomegaly, telangiectasia, localized diffuse sclerosis of bone (osteoporosis), bronchial spasm, peptic ulceration, pruritus, and dermatographia. Signs and symptoms of heparin release have not been clinically observed.

Pathophysiology

The tissue mast cells belong to the APUD system and are of neural crest origin. They synthesize histamine, store it in secretory granules, and secrete it as a local amine "hormone." In children, mastocytosis usually occurs as a localized skin lesion with mast cell infiltration. In adults, the pattern is more systemic, with mast cells proliferating to form diffuse and nodular infiltration of the liver, spleen, bone marrow, lymph nodes, and skin.

Diagnosis

When clinically suspected, the diagnosis can be confirmed by the finding of elevated levels of serum histamine and elevated levels of histamine metabolites in the urine. Biopsy confirms infiltration of mast cells.

Treatment

The treatment includes the use of antihistamine drugs and avoidance of histamine-releasing drugs. Restriction of glutin and magnesium intake is also indicated. Occasionally, irradiation of bone lesions is helpful. Chemotherapy with cyclophosphamide has been of value in some cases.[20] Patients may require appropriate treatment of secondary hypersplenism, peptic ulceration, and thrombocytopenia. The prognosis for these patients is excellent.

Ectopic Endocrine Syndromes

Ectopia refers to the rare phenomenon of clinical endocrinopathies produced by circulating humoral agents that are elaborated from unexpected sites. Almost every conceivable possibility in the spectrum of ectopia has been reported in the literature. These hormones, primarily large molecular polypeptides, have been found to emanate not only from the usual locations of endocrine and neural elements, but from tissues not usually considered to be "endocrine" (the paraneoplastic syndromes), and from mesothelial tumors not associated with an organ of any kind. The more common ectopic endocrine syndromes are summarized in Table 1.

Clinical Picture

Ectopic hormone syndromes are always the result of overproduction of amine or polypeptide hormones, usually in a precursor form. Signs and symptoms of these endocrinopathies result from the effect of the ectopic humoral agents by their stimulation of target organs. For example, in ectopic Cushing's syndrome associated with lung tumors, the excess glucocorticoids emanate from adrenal cortical hyperplasia as a consequence of overstimulation of the adrenal cortex by circulating excesses of tumor-produced ACTH.

Pathophysiology

Endocrine cells included under the APUD concept have similar embryologic origin in the neural crest and neuroectoderm, and they have common cytochemical properties. During embryogenesis they become

Table 1. *Common Ectopic Endocrine Syndromes*

ECTOPIC SYNDROME	ECTOPIC TUMOR SITES
Ectopic ACTH syndrome (ectopic Cushing's syndrome)	Lung, pancreas, thymus, thyroid (medullary), adrenal, parathyroid, gonads, liver
Ectopic hyperpigmentation (MSH)	Same as ACTH-secreting ectopic tumors
Ectopic hypercalcemic syndrome (PTH)	Lung, kidney, pancreas, lymphoma
Ectopic hyperglycemic syndrome (glucagon)	Lung, liver, kidney
Ectopic hypoglycemic syndrome (insulin)	Carcinoid, stomach, uterine cervix
Ectopic ulcerogenic syndrome (gastrin)	Carcinoid tumors of the duodenum and lung, medullary carcinoma of the thyroid, parathyroid adenoma, gastric and mesodermal tumors
Ectopic inappropriate ADH syndrome	Lung, kidney, brain, pancreas, breast, anterior pituitary, gastrointestinal tract
Ectopic gonadotropin syndrome (HCG, FSH, LDH)	Liver, ovary, lung (large cell)
Ectopic thyrotoxicosis syndrome (TSH)	Trophoblastic, gonadal choriocarcinoma, teratocarcinoma, bronchogenic carcinoma

widely and diffusely dispersed. These cells are primitively totipotent. In the course of normal development they repress all primitive capabilities other than their single normal function. When the cells become malignant, for whatever reason, there is reactivation by derepression. Renewed protein synthesis then results in "ectopic" production of large precursor molecules of polypeptide hormones. Within this concept, it is doubtful that any type of unusual endocrine secretory activity by a tumor of APUD cell origin should be termed "ectopic" at all. The lung and pancreas appear to be the most common sites of tumors that elaborate ectopic humoral agents. Cells with APUD cytology are normally present in these organs. The embryogenesis of APUD cell distribution can also explain the finding of functioning tumors in mesothelial areas, such as the insulin-like (somatomedin) secretory mesotheliomas in the retropleural and retroperitoneal spaces; developmental arrest during the usual migration of neural crest cells need only be invoked. The APUD concept, supported by the concept of derepression, thus explains most features of ectopic endocrinopathy.

Diagnosis

Several important generalizations can be made concerning the diagnosis of ectopia. If an ectopic endocrinopathy becomes apparent in a patient, the tumor is usually malignant. It is located at any site other than where it is expected to be, and electron microscopy reveals secretory granules characteristic of neuroendocrine cells. While substances elaborated by these neoplasms are biologically active, they may not be detectable by currently available radioimmunoassay techniques. In fact,

radioimmunoassay of the polypeptide that emanates from its usual site will most likely give a normal or low (suppressed) value. This is because the "ectopically" produced, biologically active humoral substances are usually heterogeneously composed of large molecular precursor forms of the normal polypeptides (such as "big gastrin") or prohormones (such as proinsulin). Their resulting endocrine effect will suppress the secretion of the *entopic* hormone. The precursor forms are difficult to measure by assay techniques. Localization of the ectopic tumor requires radiologic techniques and occasionally venous sampling of humoral products.

Treatment

Surgical and nonsurgical therapy is indicated for palliation of symptoms and possible cure of the malignant ectopic tumor, depending on its location and the presence or absence of metastases.

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Cushing's Disease: The Role of Adrenalectomy and Autotransplantation

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The clinical manifestations of Cushing's syndrome are the result of excessive glucocorticoids. Conditions causing this syndrome include: exogenous administration of adrenocorticotropic hormone (ACTH) or glucocorticoids, whether factitiously or for therapeutic purposes; benign or malignant adrenal tumors that secrete cortisol; ectopic production of ACTH by nonpituitary tumors; and hypersecretion of ACTH by the pituitary which leads to bilateral adrenal hyperplasia. Excessive secretion of ACTH owing to hyperplasia or neoplasia of the pituitary is known as Cushing's disease and is the most common cause of Cushing's syndrome if the iatrogenic use of ACTH and adrenal steroids is excluded. Orth and Liddle have defined four objectives for the ideal treatment of naturally occurring Cushing's syndrome.[12] First, clinical and biochemical evidence of the syndrome should be corrected by decreasing cortisol levels to normal. Second, functioning tumors should be removed. Third, permanent deficiency of adrenal or pituitary function should be avoided. Finally, permanent dependence on hormone replacement should not be required. These objectives can usually be achieved with operation when Cushing's syndrome results from primary adrenocortical neoplasms or from ectopic ACTH secretion if complete removal of the tumor is possible. Our ability to achieve these goals in pituitary-dependent bilateral adrenocortical hyperplasia, however, is limited, and proper management of Cushing's disease is still controversial.

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THERAPEUTIC APPROACHES

The mainstay of treatment for Cushing's disease has been bilateral total adrenalectomy. This operation results in rapid reversal of hypercortisolism and assures permanent relief of disease. However, it also leaves the patient with permanent adrenal insufficiency and lifelong dependence on exogenous steroid therapy. The risk of developing an ACTH-secreting pituitary tumor (Nelson's syndrome) has also been cited as an adverse effect of bilateral adrenalectomy in the treatment of Cushing's disease.[11] This complication, which occurs in 0 to 10 per cent of patients with Cushing's disease after bilateral adrenalectomy,[10] together with the need for steroid replacement therapy, has prompted a search for alternative methods of therapy.

The development of new therapeutic approaches to this problem has been hampered by an incomplete understanding of the pathogenesis of Cushing's disease. Harvey Cushing originally postulated that the disease was caused by pituitary tumor, and this concept has been supported by the work of several investigators.[2, 13, 15] However, pituitary tumors have not been found in all patients with Cushing's disease. Others have suggested that the disorder results from central nervous system dysfunction with overproduction of corticotropin releasing factor (CRF) by the hypothalamus.[8] Confirmation of this hypothesis requires direct measurement of corticotropin releasing factor, which is not yet possible. Clinical evidence clearly exists to support either theory, and it is possible that hypercortisolism in patients with Cushing's disease has more than a single cause.

Recent reports have stimulated interest in transsphenoidal hypophysectomy for the treatment of Cushing's syndrome.[3] Tyrrell has described his experience with a microsurgical technique in 20 consecutive patients.[15] Despite normal polytomograms in 8 patients, microadenomas were selectively resected in 17 patients, and another had a total hypophysectomy. Hypercortisolism was corrected in 17 patients, and one has persistent disease after excision of a microadenoma. Technical difficulties precluded operative evaluation of the pituitary in 2 of the 20 patients. These results were obtained by a highly skilled neurosurgical team with extensive experience in transsphenoidal microsurgery. It is uncertain, however, whether other centers with less experience can achieve similar results. Despite resolution of Cushing's syndrome, most of the patients in this study have required maintenance glucocorticoid therapy. Long-term follow-up is not yet available for this group of patients and the likelihood of recurrent disease after removal of microadenomas is unknown.

Pituitary irradiation as a treatment for Cushing's disease was introduced in the 1930s and clinical remissions have been achieved in approximately 30 to 50 per cent of patients.[1, 12] Better results have been achieved by Lawrence and co-workers using alpha particle irradiation from a linear accelerator.[9] These investigators have reported remissions in 62 per cent and significant improvement in 16 per cent of patients treated in this manner. More recently, Jennings and associates reported favorable results in 12 of 15 adolescents with Cushing's disease treated with con-

ventional cobalt therapy.[6] Despite a high remission rate, failure to control Cushing's disease still occurs in 20 to 40 per cent of patients treated with pituitary irradiation, and relapse does occur.

Several medications have been used in an attempt to decrease cortisol levels in Cushing's disease. Metyrapone, an 11-beta-hydroxylase inhibitor, will block the synthesis of cortisol but its effects are transitory owing to compensatory increase in ACTH secretion which overcomes the blockade. Another agent, o,p′-DDD, which is a derivative of the insecticide DDT, has been shown to cause necrosis of the zona fasciculata and reticularis of the adrenal cortex. This drug has been used primarily in the treatment of adrenal carcinoma but favorable results have also been reported in Cushing's disease.[2] Unfortunately, the onset of action of o,p′-DDD is slow and patient acceptance is poor owing to the attendant nausea and mental depression. It is imperative to monitor adrenal function very closely during therapy with this drug since addisonian crisis may occur. When used in Cushing's disease, the beneficial effects of this drug are derived from the fact that it produces a subtotal medical adrenalectomy. Despite encouraging reports, an insufficient number of patients have been treated with this drug to determine if this form of therapy will be associated with the high recurrence rate that characterizes subtotal surgical adrenalectomy in Cushing's disease. Cyproheptadine, a seritonin antagonist, has been heralded as an agent that corrects the basic defect in Cushing's disease.[8] Proponents of this agent believe that Cushing's disease is a central nervous system disorder and that cyproheptadine will decrease ACTH and cortisol secretion by altering serotonin pathways in the hypothalamus. Krieger has reported encouraging results in several patients treated with cyproheptadine,[8] but other investigators have not had similar success.

Our experience with these alternatives to bilateral adrenalectomy has been far from satisfactory. Of 18 patients with Cushing's disease, 11 received an alternative form of therapy in an attempt to avoid bilateral adrenalectomy. Transsphenoidal hypophysectomy was unsuccessful in one patient because of increased vascularity of the pituitary. Cyproheptadine was used in five patients with no improvement in clinical or biochemical parameters. Likewise, two patients received o,p′-DDD with little benefit. Two patients failed to respond to pituitary irradiation and two others relapsed after remissions of 1 and 11 years respectively. The phenomenon of late recurrence of Cushing's disease after "successful" radiation therapy has not received adequate attention in the literature. Our experience suggests that patients treated with pituitary irradiation should receive careful long-term follow-up so that recurrent disease can be promptly diagnosed and treated.

After unsuccessful attempts to avoid bilateral total adrenalectomy, all 18 patients underwent operation with complete remission of all manifestations of Cushing's disease and are now leading productive lives. In this group, there was no operative mortality. Increased skin pigmentation has developed in one patient, but none has evidence of a pituitary tumor. These excellent results with bilateral adrenalectomy and dissatisfaction with alternative therapies cause us to continue to support bilateral adrenalectomy as the cornerstone of treatment for Cushing's disease.

ADRENAL AUTOTRANSPLANTATION

Permanent loss of adrenal function with the necessity for hormone replacement is probably the most objectionable effect of bilateral adrenalectomy. At present we are attempting to circumvent this problem by autotransplantation of adrenal cortical tissue to an accessible site. If successful, autotransplantation could obviate the need for steroid replacement. If Cushing's disease should recur following autotransplantation, all or part of the graft could be excised under local anesthesia with little risk to the patient. Unlike most endocrine tissue, the adrenal cortex is extremely resistant to autotransplantation which has not been successfully performed in higher mammals such as the dog. Despite the lack of an adequate experimental model, Drucker et al. and Kaplan and Shires have reported successful transplantation of hyperplastic adrenal tissue into the sartorius muscle of patients with Cushing's disease treated with bilateral adrenalectomy.[4, 7] Both patients were cured, and autograft function made it unnecessary to provide hormone replacement therapy. Autotransplantation of adrenal tissue was performed in 4 of our 18 patients. One patient, described in detail below, has not received glucocorticoid or mineralocorticoid replacement for approximately one year, and has no evidence of adrenal insufficiency. Three other patients are being gradually weaned from exogenous steroids, and the functional capacity of their grafts has not yet been determined.

Case Report

A 14 year old girl was admitted to Loyola University Hospital in June, 1975 with a six-year history of recurrent nephrolithiasis, excessive weight gain, and primary amenorrhea. She was 155 cm tall and weighed 50.7 kg. Her blood pressure was 128/104 mm Hg. She had a round face, facial acne, supraclavicular fat pads, centripetal fat distribution, and pink abdominal stria. Laboratory studies showed normal blood count, urinalysis, SMA12, and serum electrolytes. Chest and skull x-ray films were normal. Baseline plasma cortisol levels were 19.8 μg per dl at 8 a.m. and 13.0 μg per dl at 4 p.m. The urinary excretion of 17-hydroxycorticosteroids was 14.3 mg per day. A low dose (2 mg per day) dexamethasone suppression test failed to decrease plasma cortisol or the urinary 17-hydroxycorticosteroids. The patient developed severe abdominal pain during two attempts to perform a high dose (8 mg per day) dexamethasone suppression test. This procedure was abandoned and an abdominal exploration with bilateral total adrenalectomy was performed on July 31, 1975. The adrenals were hyperplastic and one half of each gland was minced and transplanted into two separate areas of the left rectus abdominus muscle. The patient was discharged on the eighth postoperative day on 50 mg of cortisone acetate and 0.05 mg of 9-α-fluorohydrocortisone daily.

During the next two months her menstrual periods began and she lost 8 kg of body weight. The dose of cortisone was gradually reduced to 37.5 mg daily, and six months after surgery an ACTH stimulation test failed to increase plasma cortisol levels. During the next year, the dose of cortisone was gradually decreased to 12.5 mg in the morning and 2.5 mg in the evening. In February 1977, an 8 a.m. plasma cortisol was 8 μg per dl but there was no response to exogenous ACTH stimulation. No further decrease in replacement therapy was attempted, but eight months later an adrenal scan was performed with 1.5 mCi of 6β-^{131}I-iodomethyl-19-norcholesterol (NP59). Delayed imaging showed no uptake in the suprarenal areas but positive uptake was present at the site of the autograft in the anterior abdominal wall (Fig. 1). This evidence of graft function prompted a further reduction in her steroid replacement and she was gradually weaned from all steroid replacement over the next three months. Four months after steroid therapy was discontinued, an 8 a.m. cortisol was 19 μg per dl with a normal plasma ACTH of 97 pg per ml.

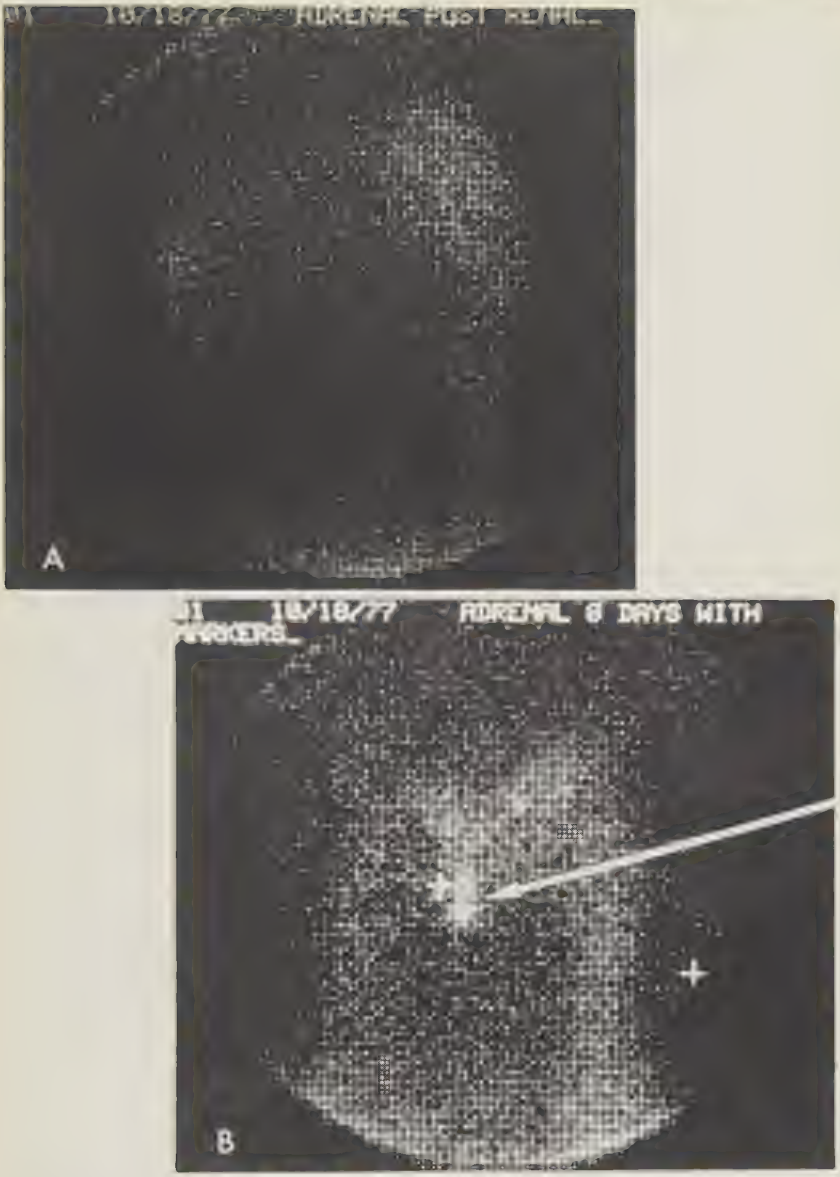

Figure 1. *A*, Delayed imaging following administration of 1.5 mCi NP-59 shows no uptake in the adrenal fossa. The only evidence of isotope activity is in the large bowel and this cleared in later images. *B*, Discrete uptake and persistent localization of NP-59 are identified in the anterior abdominal wall *(arrow)*. The area of the surgical incision has been electronically marked (+).

Autotransplantation is performed by mincing half of each gland into fine pieces which are then placed into a well vascularized muscle bed. When the adrenals have been removed transabdominally, we have placed the autograft in the rectus abdominis muscle. When a posterior approach was used for adrenalectomy, we have placed the autograft in the paraspinal muscles.

As illustrated by the case report, one of the major problems in adrenal autotransplantation is evaluation of the functional capacity of the graft so that the patient can be safely weaned from exogenous steroids. Biopsy has been used to determine graft viability, but this is an invasive procedure which sacrifices valuable tissue and has the risk of compromising the blood supply to the remaining tissue with loss of graft function. In addition, histologic demonstration of adrenal cells does not necessarily imply normal graft function. Exogenous ACTH stimulation has usually been unsuccessful in determining autograft function since it often fails to increase plasma cortisol levels while the patient is on maintenance steroid therapy. Lack of response may be owing to the fact that the test is performed before the transplanted cells have become functional or to the fact that the graft is maximally stimulated by the high levels of endogenous ACTH found in Cushing's disease after bilateral adrenalectomy. Kaplan and Shires[7] attempted to document function of the autograft by obtaining simultaneous measurements of plasma cortisol from the femoral vein above the site of the autotransplant in the sartorius muscle and from the antecubital vein. A difference was detected and the patient was successfully weaned from exogenous steroid therapy.

Adrenocortical imaging with NP-59 is of value in the localization and differential diagnosis of the various causes of Cushing's syndrome and in the identification of adrenal remnants after bilateral adrenalectomy.[14] This technique can also be used to evaluate the viability of adrenal transplants since the isotope is taken up by the tissue and used for glucocorticoid synthesis. This scanning technique has the added advantage of proving that adrenal remnants are not the cause of cortisol secretion after adrenalectomy and autotransplantation.

Recurrence of Cushing's disease is a well known problem in subtotal adrenalectomy and has been reported by Hardy after autotransplantation of adrenal tissue.[5] In contrast to subtotal adrenalectomy in which major operative intervention is required if recurrence develops, the autotransplant is readily accessible and can be easily removed if necessary. If recurrence develops, an adrenal scan should be performed before the graft is removed to determine the site of excessive cortisol synthesis, since recurrent disease has developed as a result of hyperplasia of adrenal remnants in the retroperitoneum.

CONCLUSION

Bilateral adrenalectomy is a rapid and permanent means of reversing the hypercortisol state in Cushing's disease. The safety and effectiveness of this operation are such that it should remain an integral part of the treatment of Cushing's disease.

Autotransplantation of adrenocortical tissue has been shown to be feasible in patients with Cushing's disease. Continued development of this technique may make it possible to avoid total loss of adrenal function with bilateral adrenalectomy. Adrenal scanning with NP-59 can demonstrate graft function and aid in weaning patients from exogenous glucocorticoid therapy.

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Transplantation of the Parathyroid Glands: Current Status

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It is remarkable that Halsted began his basic and clinical experiments on parathyroid transplantation within 20 years after the glands were discovered. Over the past five years, the clinical utility of parathyroid transplantation has been explored. During this time our group has grafted over 75 patients. The survival and function of parathyroid autografts and allografts have been well documented and the technique of successful cyropreservation has been established. Parathyroid transplantation is not indicated in the majority of patients with parathyroid hyperfunction, but the technique provides the surgeon with great flexibility in confronting certain unique problems that patients with hyperparathyroidism may present. This report will outline the clinical indications for parathyroid transplantation. Also, the techniques of parathyroid grafting and cryopreservation will be described and the clinical results reviewed.

INDICATIONS FOR PARATHYROID TRANSPLANTATION

Even though we will discuss several clinical indications for transplanting parathyroid glands, it should be stated that we consider this technique still to be an experimental procedure. Only after extended follow-up of grafted patients can firm conclusions be drawn regarding the technique's utility.

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Autotransplantation

RENAL OSTEODYSTROPHY (SECONDARY HYPERPARATHYROIDISM). The prolonged survival of patients with renal insufficiency has been afforded by the institution and widespread use of hemodialysis. A well recognized complication that may occur in patients with chronic renal failure is the development of renal osteodystrophy or secondary hyperparathyroidism. While the majority of patients with this disorder can be successfully managed medically, a few are refractory to such conservative therapy. The development of skeletal fractures, intractable pruritus, or metastatic calcification of the vascular system or soft tissues is an indication for parathyroidectomy. There has been controversy regarding the preferred operative management of these patients. Some clinicians have argued that they are best treated by total parathyroidectomy and permanent vitamin D and oral calcium replacement therapy, whereas others have maintained that radical subtotal (three and one half glands) parathyroidectomy is the treatment of choice. Even with the latter procedure, some patients will become aparathyroid if the remnant of residual gland in the neck fails to function, and they, too, will require vitamin D and calcium maintenance. Conversely, should the parathyroid remnant remaining in the neck become hyperfunctional and symptoms of renal osteodystrophy return, repeat exploration of the neck may be required. The choice then is to remove the remaining fragment of gland and render the patient aparathyroid or resect a portion of it hoping to establish the euparathyroid state.

In 1975, we proposed that a suitable alternative to both of these procedures might be total parathyroidectomy and concomitant heterotopic autotransplantation of parathyroid tissue to the forearm muscle.[1] Such patients would have their parathyroid mass reduced; however, should graft-dependent hypercalcemia subsequently develop, a portion of the implanted tissue could be removed under local anesthesia. Graft failure was not anticipated since previous experiments in several species of laboratory animals had consistently demonstrated that autotransplanted parathyroid tissue would maintain the previously aparathyroid recipient in a normocalcemic state.[7, 10, 12]

PRIMARY PARATHYROID HYPERPLASIA. In patients with familial hyperparathyroidism or multiple endocrine neoplasia type I or II, generalized (four glands) parathyroid enlargement is common. These patients obviously require a more aggressive surgical approach than do patients with hyperparathyroidism caused by disease of a single gland. The most commonly employed surgical procedure has been radical subtotal parathyroidectomy. Results utilizing this technique have varied. Generally, recurrent hyperparathyroidism has developed in approximately 10 to 30 per cent of patients.[6] However, Castleman and Cope reported an incidence of recurrent hypercalcemia of 55 per cent in their patients with water clear cell hyperplasia following parathyroidectomy of three and one half glands, and stated that they had not cured a single patient.[5] Bruining et al.[4] and Seyfer and associates[8] reported a 25 to 50 per cent incidence of postoperative hypocalcemia with this procedure. In an

effort to circumvent these complications, we explored the use of total parathyroidectomy and forearm autotransplantation in these patients.

TOTAL THYROIDECTOMY FOR CARCINOMA. The incidence of postoperative hypoparathyroidism in patients undergoing total thyroidectomy for carcinoma ranges from 10 to 50 per cent.[1] It is usually assumed that viable parathyroid tissue is present after thyroidectomy; however, occasionally hypocalcemia develops which may become permanent. This complication is theoretically preventable, for if the surgeon locates the parathyroid glands at the time of thyroidectomy and autografts those whose viability is questionable, the likelihood of the patient developing subsequent hypocalcemia is minimized. The reader should not interpret this statement to mean that total parathyroidectomy and autotransplantation are recommended for all patients undergoing total thyroidectomy. Only those patients whose parathyroid glands have to be removed with the thyroid or whose vascular supply is compromised should be grafted. Intact healthy parathyroid tissue should remain in situ. The resected parathyroid glands can readily be transplanted into the sternocleidomastoid muscle. This site is chosen because it is in the operative field, and the likelihood that normally functioning parathyroid tissue will have to be removed subsequently because of excessive function is remote. It should be remembered, however, that 40 to 60 per cent of patients with multiple endocrine neoplasia type II and medullary thyroid carcinoma have parathyroid hyperplasia. In those patients with multiple endocrine neoplasia II who require total thyroidectomy, we have customarily autografted their resected enlarged parathyroid glands to the forearm. Thus, ready access is provided to the transplanted tissue should removal of a portion of the graft be subsequently required.

RECURRENT OR PERSISTENT HYPERPARATHYROIDISM. One of the most difficult problems encountered by the surgeon is the development of hypercalcemia in a patient previously explored for hyperparathyroidism. Persistent rather than recurrent hyperparathyroidism is the more common complication. Usually these unfortunate patients remain hypercalcemic immediately after surgery, rather than developing an elevated serum calcium concentration after months or years of normocalcemia. At the initial surgery, either the enlarged parathyroid glands are not identified or generalized parathyroid enlargement is not appreciated, and inadequate tissue is resected. Even though the surgeon performing the neck reexploration finds an enlarged parathyroid gland, the problem cannot be considered to be resolved, as often one is unsure whether this is the only remaining parathyroid gland or whether viable tissue resides elsewhere in the neck. If it is known and histologically documented that three or three and one half parathyroid glands have been removed at previous surgery, and if at the time of repeat neck exploration a fifth gland cannot be found, the remaining parathyroid tissue can be autografted to the forearm muscle. If, however, one is unsure of whether residual parathyroid tissue resides in the neck, it is wise to cryopreserve resected parathyroid tissue by a technique described subsequently. One can then observe the patient in the postoperative period. If the patient becomes normocalcemic, no further treatment is indicated. If, however, the patient

has been rendered aparathyroid, plasma calcium concentration will fall and continuous vitamin D and calcium replacement will be required. In this situation, the cryopreserved autologous parathyroid tissue can be thawed and the patient grafted under local anesthesia. It has been demonstrated in animals[12] that parathyroid tissue can be viably cryopreserved for 9 to 12 months, and Brennan[2] has recently demonstrated in humans that parathyroid tissue can be viably frozen for as long as 18 months. Under most circumstances, a period of cryopreservation less than six months would be sufficient for one to decide if parathyroid grafting were necessary.

LARYNGECTOMY FOR CANCER. Although the occurrence of hypoparathyroidism in patients undergoing total laryngectomy for carcinoma is unusual, occasionally the thyroid and parathyroid glands are resected en bloc with the larynx, and dual hormone deficiencies develop. Hypothyroidism is relatively easily managed with L-thyroxine replacement, whereas the medical management of hypoparathyroidism is complicated. If the operating surgeon identifies the parathyroid glands to be resected and autografts them to a nearby muscle bed, the incidence of hypoparathyroidism is greatly reduced.

Parathyroid Allotransplantation

Parathyroid allotransplantation is rarely indicated. The pharmacologic immunosuppression required for successful allotransplantation presents a potentially greater risk of morbidity than the vitamin D and oral calcium replacement therapy. In patients with DiGeorge's syndrome, a disease characterized by absence of the pharyngeal pouch derivatives (parathyroids and thymus), parathyroid allotransplantation could theoretically be accomplished without immunosuppression.

METHOD

The Technique of Parathyroid Transplantation

The method of implanting parathyroid tissue is uniformly the same for both autograft and allograft, for sternocleidomastoid muscle and brachioradialis implants, and for both fresh and frozen tissues. Upon removal of the parathyroid tissue, it is immediately placed into a chilled medium. Whereas we formerly used isotonic tissue culture media (such as Eagle's, Hank's, Earle's, RPMI 199, Waymouth's), we have subsequently found that saline at 4°C is sufficient. The medium is contained in a receptacle on an ice bath which is prepared by placing sterile Vi-drape over a splash basin filled to heaping with crushed ice (Fig. 1). After 20 or 30 minutes of chilling, the parathyroid tissue will become firm and can be sliced into 1 by 3 mm pieces. Approximately 20 of these slivers are then transplanted into the selected muscle bed in an area measuring about 5 by 5 cm (Fig. 2). Each piece is implanted in a separate muscle pocket. The fascia and superficial muscle overlying each parathyroid piece are then closed with a nonabsorbable suture. The suture serves to secure the transplanted parathyroid in its pocket, and also marks the site of the implant should

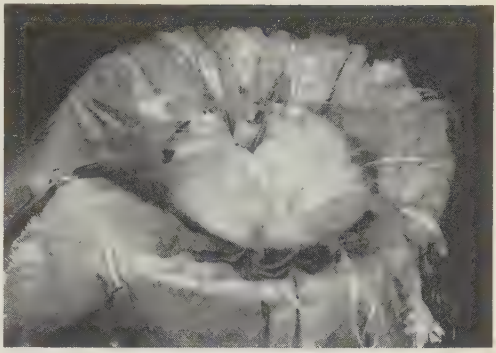

Figure 1. A sterile ice bath is prepared for holding the parathyroid glands. One receptacle in the foreground is for the parathyroid tissues and the other is for the instruments used for slicing the parathyroid glands.

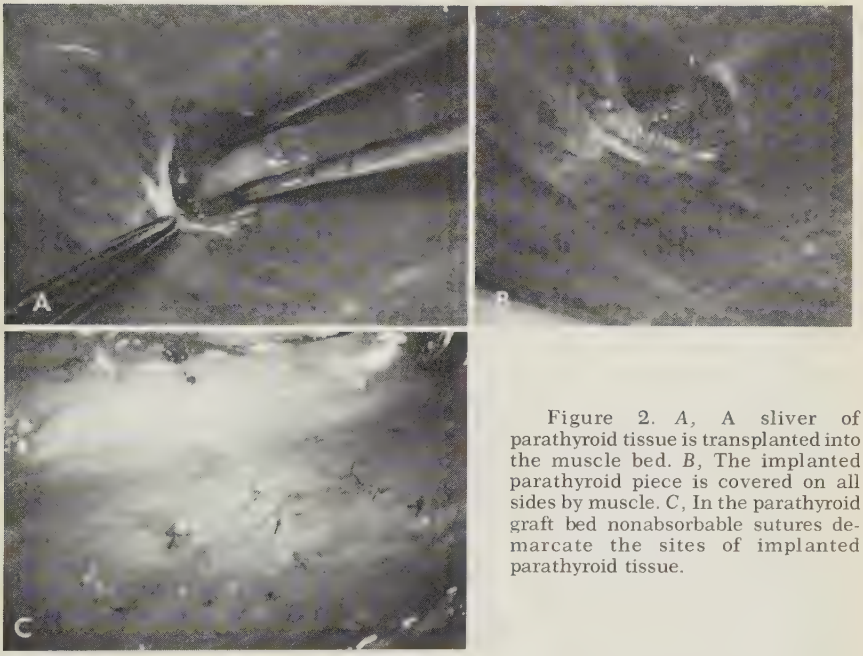

Figure 2. *A*, A sliver of parathyroid tissue is transplanted into the muscle bed. *B*, The implanted parathyroid piece is covered on all sides by muscle. *C*, In the parathyroid graft bed nonabsorbable sutures demarcate the sites of implanted parathyroid tissue.

subsequent removal be required for the development of graft-dependent hypercalcemia.

Parathyroid Cryopreservation

At the time of surgery, the parathyroid tissue is prepared as above, being sliced into 1 by 3 mm pieces. These are then placed into 3 dram vials (10 pieces to a vial) containing 3 ml of a solution composed of 10 per cent dimethyl sulfoxide, 10 per cent human serum, and 80 per cent tissue culture medium. The vials, usually a total of four or five, are then placed into a controlled rate freezer (Union Carbide Corporation, Linde Division, Indianapolis, Indiana) and frozen at a rate of −1°C per minute down to a temperature of −100°C. The vials are then placed into an LR 1000 liquid nitrogen freezer (Union Carbide, Linde Division) and maintained at a

temperature of −200°C. At the time of thawing, the vials are immediately placed into a 37°C water bath and gently agitated until the last ice crystals disappear. The vials are then removed and the parathyroid tissue washed two or three times in tissue culture medium in an attempt to remove the dimethyl sulfoxide which is toxic at room temperature. The sterile pieces are then ready for implantation. A large majority of our patients undergoing surgery for hyperparathyroidism have parathyroid tissue cryopreserved at the time of surgery. This provides an auxiliary source of tissue should the graft bed become infected or should the parathyroid tissue fail to function. The rationale for cryopreserving parathyroid tissue in patients undergoing reexploration for recurrent or persistent hyperparathyroidism has been covered previously.

Postoperative Management of Patients Receiving Parathyroid Transplants

In the immediate postoperative period, care is taken not to draw blood from the antecubital vein and not to inflate a blood pressure cuff above the graft site. Skin sutures are removed at seven days. The serum calcium concentration is measured daily, and is allowed to drop to a level of about 7 mg per dl or until the patient becomes uncomfortable from tingling or cramps. Generally, because of the severe bone disease, patients with renal osteodystrophy have a much more rapid and prolonged drop in the serum calcium concentration than patients with primary hyperparathyroidism. Intravenous calcium gluconate may be required for several days. Oral vitamin D (dihydrotachysterol, 0.6 mg per day tapering to a maintenance dose of 0.125 mg per day) and calcium (glubionate calcium, 15 cc four times a day) replacement therapy are begun on the third or fourth postoperative day. In patients with primary hyperparathyroidism, the dihydrotachysterol is usually stopped at four weeks, and if the serum calcium concentration remains normal, the oral calcium is stopped two weeks thereafter. Generally, patients who have undergone total parathyroidectomy and receive grafts for renal osteodystrophy require a much longer period of replacement therapy than do patients with primary hyperparathyroidism. In some of our patients with severe secondary hyperparathyroidism, replacement therapy has been required for more than a year.

Assessment of Parathyroid Graft Function

There are several ways of ascertaining whether the transplanted parathyroid tissue is functioning. The sine qua non of a functioning autograft is that the host can be maintained in a normocalcemic state with no replacement therapy, and with the grafted tissue as the only source of parathyroid hormone. A simple way to evaluate graft function is to determine the level of parathyroid hormone in the antecubital vein draining the parathyroid graft bed and compare it with the PTH level in the antecubital vein of the opposite arm. Almost always, PTH levels in the antecubital vein blood of the grafted arm are two- to tenfold higher than PTH levels in the nongrafted arm. Finally, a biopsy specimen from one of the implanted parathyroid pieces can be examined histologically. Although parathyroid graft biopsies were done routinely early in our series, we rarely use this

method to assess graft function today. Although we have not routinely measured antecubital vein PTH levels in the immediate postoperative period, we have noted elevated hormone values in graft venous effluent as early as 7 to 10 days after surgery. Once vitamin D and calcium replacement therapy have been stopped and it is assured that patients have a functioning autograft, they are evaluated at six month intervals.

Management of the Patient with Graft-Dependent Hypercalcemia

In 10 to 15 per cent of the patients whom we have grafted, hypercalcemia has developed in the postoperative period, usually three months to two years after surgery. We have not performed partial graft resections in patients with serum calcium concentrations between 10.5 and 11.0 mg per dl providing they are asymptomatic with no hypertension or hypercalciuria. Conversely, in patients who have serum calciums in excess of 11 mg per dl, we routinely excise one-half of the implanted parathyroid pieces under local anesthesia. This is almost always sufficient to cause a decrease in the serum calcium concentration to the normal range. Brennan and associates, however, recently reported a patient with a parathyroid adenoma autografted to the forearm.[3] This patient required resection of a portion of the grafted parathyroid tissue on two occasions to lower the serum calcium concentration, and even then the serum calcium values were at the upper limit of normal.

RESULTS

Renal Osteodystrophy

Of approximately 40 patients recently evaluated after total parathyroidectomy and autotransplantation, 85 per cent reported symptomatic improvement in bone pain and/or pruritus. Seven per cent reported no change in symptoms, and 8 per cent reported a worsening of symptoms.

Eighty-seven per cent of the patients had normal serum calcium concentrations once the vitamin D and oral calcium replacement therapies were stopped. Thirteen per cent had normal serum calcium concentrations, but still required calcium and vitamin D replacement therapy. Almost all of these patients were in the first year following parathyroidectomy, and we expect them ultimately to tolerate withdrawal of replacement therapy.

Approximately 90 per cent of patients with renal osteodystrophy who have undergone total parathyroidectomy and heterotopic autotransplantation have demonstrated a higher concentration of parathyroid hormone in the antecubital vein of the grafted compared with the nongrafted arm. Of those patients who have no gradients demonstrated, many are nevertheless normocalcemic off of vitamin D and calcium replacement therapy. We have also noticed this phenomenon in patients who have received parathyroid transplants for primary parathyroid hyperplasia. Apparently there is an altered venous drainage, and even though the graft is functioning, an elevated PTH level cannot be detected in the graft bed venous effluent.

Over the last two years, we have begun to perform total parathyroidectomy and autotransplantation of parathyroid tissue in children with renal osteodystrophy. The case report of such a child is described below:

A 13 year old Caucasian boy had presented in infancy with congenital posterior urethral valves. He underwent numerous urologic procedures in the first year of life including a right nephrectomy. He had a transient left nephrostomy tube until his urethral valves were resected. Despite urinary reconstructive procedures, the child continued to have a progressive loss of renal function. By the age of 12 years, he was maintained on a conservative medical regimen exclusive of dialysis. In October, 1977, he had a creatinine clearance of 15 ml per minute. Over the previous year, the patient experienced increasing bone pain, stiffness, weakness, proximal muscle wasting, and pruritus. Skeletal x-ray films demonstrated changes compatible with renal osteodystrophy.

On physical examination, the patient was cachectic, his height was 141 cm, and his weight was 36.3 kg (less than the third percentile). His pulse was 110, blood pressure 120/70, and temperature 37.0°C. Ecchymoses and excoriations were noted on the skin.

Hemoglobin was 7.7 gm per dl, white blood cell count was 6900 per mm^3, BUN was 97 mg per dl, sodium 143 mEq per liter, potassium 4.2 mEq per liter, CO_2 14 mm per liter, chloride 107 mEq per liter, creatinine 8.4 mg per dl, calcium 8.9 mg per dl, phosphorus 5.8 mg per dl, and alkaline phosphatase 880 IU. On October 24, 1977, the patient underwent a total parathyroidectomy and autotransplantation of parathyroid tissue to the right forearm. In the postoperative period, the serum calcium dropped to 5.8 mg per dl. He was placed on intravenous calcium in a dose of 7 gm per day, and by the sixth postoperative day, the serum calcium was 7.9 mg per dl. He was discharged on the ninth hospital day on glubionate calcium, 50 cc orally four times a day, dihydrotachysterol, 0.5 mg daily, and aluminum hydroxide gel capsules, 475 mg three times a day. At the time of discharge, his alkaline phosphatase had risen to 1380 IU. A biopsy of the iliac crest taken at surgery showed active and inactive resorption surfaces throughout the specimen on microradiograph. Broad areas of hypomineralization within the cortex suggested prolonged mineral deficiency. On stained section, there were marrow fibrosis and areas of active osteoclastic resorption. Otherwise, marrow elements appeared normal. On unstained sections, bone formation was normal to low for age and most osteoid seams lacked a demineralization front. The findings were compatible with secondary hyperparathyroidism.

The patient improved markedly in the first three to four weeks after surgery with a reduction in bone pain and pruritus. A metabolic bone survey two months after surgery showed healing of the previously noted periosteal resorption of the hands and tibial shafts. The plasma alkaline phosphatase was 1000 IU. The plasma PTH in the grafted arm was 0.29 ng per ml, compared with a PTH level in the ungrafted arm of less than 0.02 ng per ml. The serum concentration of alkaline phosphatase continued to fall and by seven months postoperatively was 320 IU. The patient remained on moderate doses of vitamin D and calcium replacement. At present, he is fully active and essentially asymptomatic. Whereas he grew a total of 4 cm in height during the 12 months preceding surgery, he has grown 8 cm in the year since surgery, despite a continued deterioration in renal function as evidenced by a BUN increase to 147 mg per dl and a fall in creatinine clearance 8 ml per min. Presently he is a candidate for renal allotransplantation.

Primary Parathyroid Hyperplasia

We have grafted 24 patients with primary parathyroid hyperplasia. Eight (33 per cent) of the 24 patients with primary hyperparathyroidism had undergone neck exploration previously and were being reoperated for recurrent or persistent hyperparathyroidism. Twenty-three (96 per cent) of the 24 currently require no vitamin D or calcium replacement therapy.

One patient (4 per cent) requires oral vitamin D and calcium replacement therapy, despite the demonstration of higher concentrations of PTH in the antecubital vein of the grafted arm compared to the nongrafted arm. This patient underwent a total gastrectomy for the Zollinger-Ellison syndrome after parathyroidectomy, and it is questioned whether his calcium absorption is compromised.

Twenty-two of the 24 patients (92 per cent) had demonstrated increased concentrations of parathyroid hormone in the antecubital vein draining the grafted compared with the nongrafted arm. In two recently grafted patients, gradients have not yet been defined.

Development of Graft-Dependent Hypercalcemia

Six patients (three with primary parathyroid hyperplasia and three with secondary parathyroid hyperplasia) have developed graft-dependent hypercalcemia in the postoperative period. The three patients with renal osteodystrophy have had half of their graft removed. Two are currently normocalcemic and are free of the signs and symptoms of renal osteodystrophy. In the third patient who developed calciphylaxis, all of the grafted parathyroid tissue was removed. This patient is now on vitamin D and oral calcium replacement therapy. Two of the three patients with primary parathyroid hyperplasia have undergone resection of a portion of the parathyroid graft. One of these patients is normocalcemic; however, the other has persistent hypercalcemia. At this latter patient's original surgery, three parathyroid glands were resected and one left intact. Since hypercalcemia persisted, the remaining parathyroid gland was resected and autografted to the forearm. The patient has remained hypercalcemic following resection of half of the grafted tissue and it is felt that an accessory hyperfunctioning gland exists in the neck. The remaining patient with primary parathyroid hyperplasia who has graft-dependent hypercalcemia has a serum calcium concentration between 10.5 and 11.0 mg per dl. He is not hypercalciuric, and the decision has been made to manage him conservatively.

Total Thyroidectomy for Carcinoma

Twelve patients with thyroid carcinoma (eight with medullary carcinoma and four with either papillary or follicular carcinoma) have undergone total thyroidectomy. The viability of the parathyroid glands could not be assured in these patients, and, therefore, each had 20 parathyroid pieces transplanted to the sternocleidomastoid muscle. All are currently normocalcemic without vitamin D or calcium replacement therapy.

Parathyroid Allotransplantation

A previously reported patient with renal osteodystrophy underwent total parathyroidectomy and subsequently received a renal allograft from his father.[11] The transplanted kidney functioned well; however, because of marked hypocalcemia refractory to medical management, the patient received two of his father's parathyroid glands as an allograft to the

forearm muscle. The transplanted tissue functioned for three years; however, the patient subsequently rejected both the kidney and the parathyroid tissue. He again required vitamin D and calcium replacement therapy, and recently died from progressive renal disease. Two patients with DiGeorge's syndrome have received parathyroid allografts; however, neither has survived long enough to allow graft function to be assessed.

DISCUSSION

Currently, there seems to be general agreement that patients with primary hyperparathyroidism caused by a single enlarged parathyroid gland are best managed by a conservative approach of removing that gland and perhaps obtaining a biopsy specimen of one other gland. In patients who have hyperparathyroidism owing to generalized enlargement of four parathyroid glands, the procedure most commonly used has been radical, subtotal (three and one half glands) parathyroidectomy. The experience with this operative procedure has been varied with some authors reporting a relatively low incidence of hypoparathyroidism and recurrent hyperparathyroidism, whereas others have described unsatisfactory results. It is primarily for these reasons and because of our own relatively unsatisfactory experience with three and one half gland parathyroidectomy in patients with parathyroid hyperplasia that we began to perform total parathyroidectomy with autotransplantation of parathyroid tissue to the forearm muscle. This technique appears to be especially useful in managing patients with recurrent or persistent hyperparathyroidism following an initial unsuccessful neck exploration. Should only one or one half parathyroid gland remain, then resection of this will render the patient aparathyroid and on permanent vitamin D and calcium replacement therapy. The availability of a method of storing the parathyroid tissue in a frozen viable state while the status of the patient is being defined provides the surgeon with the ability to implant the autologous tissue if necessary.

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Index

Page numbers of symposium and article titles are given in **boldface** type.

ADENOMATOSIS, multiple endocrine, hormone production and, 103
Adrenal cortex, autotransplantation of, in Cushing's disease, 162–164
Adrenal medulla, carcinoma of, 98–99
Adrenalectomy, in Cushing's disease, 160–161
Adrenocortical imaging, in Cushing's disease, 164
Angiography, in localization of insulinoma, 122–123
  in localization of pancreatic tumors, 133
Antithyroid drugs, 36
APUD cell system, carcinoid tumors of, bronchial, 145
    drug therapy of, 147–148
    gastric, 145
    midgut, 144
    pancreaticoduodenal, 145–146
    surgical treatment of, 147
  characteristics of, 93–94
  diarrheogenic syndromes of, 143–153
  embryogenesis of, 94
  hyperplasia in, 100
  immunocytochemical aspects, 102–105
  paraganglioma of, 154
  pathobiology of secretion in, 94
  somatostatinoma of, 153
  tumors of, **93–108**
    ectopic, 155–157
    mastocytosis syndrome, 155
    uncommon, **143–158**
  watery diarrhea, hypokalemia, achlorhydria syndrome of, 148–150
Aspiration biopsy cytology, of thyroid gland, **3–18**
Aspiration therapy, in cystic thyroid lesions, 30

BIOPSY, needle, versus needle aspiration biopsy, 6
  needle aspiration, aspiration biopsy cytology technique, 4–7

CALCIUM, infusion of, in diagnosis of insulinoma, 122
Carcinoma, of adrenal medulla, 98–99
  of gastrointestinal chromaffin cells, 99
  of islet cells, 96–98, 103, 120, 133
  of thyroid gland, aspiration biopsy cytology diagnosis of, 9–11
  treatment of, 17
Chromaffin cells, gastrointestinal, carcinoma of, 99
C-peptide assays, in diagnosis of insulinoma, 121
Cushing's disease, adrenalectomy and autotransplantation in, **159–165**

DIARRHEOGENIC syndromes, of APUD system, 143–153
Drugs, antithyroid, for Graves' disease, 36
Dysplasia, bronchial epithelial, APUD cell system and, 101

ECHOGRAPHY. See *Ultrasonography.*
Endocrine surgery, symposium on, **3–177**
Epidermis, lesions of, in pancreatic glucagonoma, 139–140

GOITER, ultrasound diagnosis of, 19–33
colloid, aspiration biopsy cytology diagnosis of, 8
Graves' disease, antithyroid drugs for, 36
propranolol for, 39–40
radioactive iodine therapy for, 36–38
subtotal thyroidectomy for, 40–41
surgical treatment, 38–41
thyroidectomy for, **35–44**

HASHIMOTO'S disease, radiation exposure as a cause of, 67, 68
Hormones, visualization techniques, 102–105
5-Hydroxyindoles, hyperproduction of, in carcinoid tumors of the APUD cell system, 146
Hyperparathyroidism, primary, and irradiation of thyroid gland, **65–75**
recurrent or persistent, parathyroid transplant in, 169
with concurrent thyroid disease, 72–74

INSULINOMA, angiography and, 122–123
C-peptide secretion in, 121
diagnosis and treatment of, **119–129**
diagnosis of, radioimmunoassay for, 119, 132
surgical technique for removal, 126–128, 134–135
^{131}Iodine, for thyroid scintigraphy, 12
Islet cells, carcinoma of, morphology, 96–98
proinsulin secretion in, 96–97, 120
pancreatic, gastrinoma of, 136–138
insulinoma of, 134–136
tumors of, **131–141**

KULCHITSKY'S cells, carcinoma of, 100

METHIMAZOLE (Tapazole), for Graves' disease, 36, 39
Mucosal neuroma syndrome, **109–118**
Multiple endocrine adenomatosis (MEA), hormone production and, 103
Multiple endocrine neoplasia type IIb, **109–118**

NESIDIOBLASTOSIS, as a disease of APUD cell system, 100, 104

OAT cell carcinoma, as a disease of APUD system, 100, 105

PANCREAS, insulinomas of, **119–129**
islet cell tumors of, **131–141**
polypeptide abnormalities of, diarrheogenic syndrome in, 152
tumors of, tests for localization, 133
Pancreatectomy, hypoglycemia following, 135
Parathyroid, allotransplant of, 170, 175
autotransplant of, 80, **167–177**
assessment of graft function, 172
carcinoma of, surgery for, 66
cryopreservation of, 80, 171
transplant of, **167–177**
Parathyroid disease, surgery for, 77–81
complications, **83–92**
Propranolol, for Graves' disease, 39–40
Propylthiouracil (PTU), for Graves' disease, 36, 39

RADIATION, as a cause of thyroid cancer, 47–49
hazards of, 45–46
simultaneous occurrence of hyperparathyroidism and thyroid nodules after exposure to, **65–75**
Radioactive iodine therapy, for Graves' disease, 36–38
Renal osteodystrophy, parathyroid transplant in, 168, 173

^{99m}TECHNETIUM pertechnetate scintigraphy, in thyroid scan, 12, 59
Thyroid crisis, thyroidectomy and, 84
Thyroid, adenoma of, ultrasonic characteristics, 24
anatomy, ultrasonic, 22
carcinoma of, as a result of radiation therapy, 47–49
hyperparathyroidism and radiation and, **65–75**
medullary, diarrheogenic syndrome in, 151
hormone production and, 103
surgery for, 67, 88
tests for, 50–51
cysts of, 17
ectopic subhyoid, ultrasonic characteristics, 28–29
irradiation of, **45–63**
post-radiation management of patients, 52
lesions of, cystic, aspiration therapy of, 30
ultrasonic diagnosis, 23
diffuse, ultrasonic diagnosis, 26–28
ultrasonographic measurement, 31
mixed, ultrasonic diagnosis, 25
solid, ultrasonic diagnosis, 25
nodular disease, aspiration biopsy cytology in, **3–18**
following radiation therapy, 47
surgery for, 52–57

Thyroid (*Continued*)
radiation exposure and hyperparathyroidism and simultaneously occurring nodules, **65–75**
scintigraphy of, 12, 14–15
tumors of, aspiration biopsy cytology, 4–11
technique of puncture, 4
ultrasonic diagnosis, 19–33
Thyroid disease, surgery for, complications, **83–92**
hypoparathyroidism and, 88–92
Thyroid scan, 58
Thyroidectomy, for carcinoma, parathyroid transplant in, 169, 175
hypocalcemia and, 89–91
in Graves' disease, **35–44**
clinical evaluation of, 41–42
complications of, 40–41
myxedema and, 88
nerve injury and, 85–87
thyroid suppression therapy following, 88
Thyroiditis, diagnosis of, aspiration biopsy cytology technique, 8

Ulcer diathesis, pancreatic islet cell tumors and, 136
Ultrasonography, acoustic principles of, 19
of thyroid, **19–33**
technology of, 20

Whipple's triad, in insulinoma, 119

Zollinger-Ellison syndrome, gastrinoma and, 137–138

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